

## CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA: 21-236

Submission Dates: January 2, 2001  
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June 7, 2001

Drug Name: **IntraDose (Cisplatin/Epinephrine Injectable Gel)**

Applicant: Matrix Pharmaceuticals, Inc.  
Fremont, CA

Reviewer: Sophia Abraham, Ph.D.

Submission Type: Review of an Original NDA

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### I. EXECUTIVE SUMMARY

This is a review of an NDA filed for IntraDose (cisplatin/ epinephrine, CDDP/epi) Injectable Gel. The Applicant seeks approval for the use of IntraDose in the treatment of patients with recurrent squamous cell carcinoma of the head and neck (SCCHN) whose tumors considered incurable with surgery or radiotherapy. The proposed dosing schedule is 0.25 ml IntraDose per  $\text{cm}^3$  of tumor volume to a maximum of 10 ml (40 mg cisplatin) to be administered weekly for up to six treatments (one cycle). In support of the proposed indication (i.e., use of IntraDose in the treatment of SCCHN), the Applicant submitted two prospective, randomized, multicenter, double-blind, placebo-controlled Phase III studies (Studies 414-94-2 and 514-94-2). A total of 178 patients with tumor volumes up to  $20 \text{ cm}^3$  were enrolled and randomized (2:1) to receive IntraDose or placebo (collagen gel only). The primary clinical endpoints were objective response of a target tumor and the attainment of clinical benefit. The pharmacokinetics (PK) of total and free platinum (Pt) in patients with head and neck cancer were assessed following intratumoral administration of IntraDose in the pivotal Study MP #516-99-PK.

IntraDose was granted an Orphan Drug Designation for this indication on April 3, 2000. No other approved therapy is available for the proposed indication (i.e., SCCHN). Foscan is a competing product under development for the treatment of SCCHN.

## (A) OVERALL RECOMMENDATION

The NDA 21-238 filed for the use of IntraDose in the treatment of patients with recurrent squamous cell carcinoma of the head and neck appears to be acceptable from the Clinical Pharmacology and Biopharmaceutics perspectives. High variability in cisplatin pharmacokinetics after IntraDose administration needs further investigation. The Applicant should incorporate the changes made in the Clinical Pharmacology/ Pharmacokinetic section of the package insert as outlined under section "I.B" of this review.

Please forward the Overall Recommendation (section I.A.), Labeling Recommendations (section I.B.), and Comments 1 and 2 (section I.C.) to the firm. Comments 3-5 are to the Medical Reviewer (section I.C.).

## (B) LABELING RECOMMENDATIONS

Please incorporate the changes made in the CLINICAL PHARMACOLOGY/ PHARMACOKINETICS section of the package insert for IntraDose as outlined below:

[Note: Statements added are in italic and bold. Statements deleted are strikeout]

### CLINICAL PHARMACOLOGY

#### Pharmacokinetics

In a pharmacokinetic study of IntraDose administered intratumorally to sixteen subjects Study 516-99-PK (total of 20 treatments) with squamous cell carcinoma of the head and neck, platinum levels were monitored in plasma (total Pt), and plasma ultrafiltrate (free Pt). ***The pharmacokinetics of both total and free platinum were determined in 16 patients with squamous cell carcinoma of the head and neck following intratumor administration of IntraDose.*** Patients received 0.25 mL gel/cm<sup>3</sup> of tumor volume, corresponding to cisplatin doses of ***6.8-16.4 mg/m<sup>2</sup>*** 40.5 to 25.6 mg (averaging approximately 10 mg/m<sup>2</sup>) body surface area. After the first dose, the ***peak*** maximum average total Pt ***platinum*** concentration in the plasma was reached at ***a median (range) t<sub>max</sub> value of 1.5 (0.08-24) hours*** was observed reached at 9.8 hours. Over the dosing this dose range ***administered***, average observed total Pt ***platinum*** peak plasma concentration (C<sub>max</sub>) ***averaged ("standard deviation) 250"85 ng/mL*** was 252 ng/mL and decreased slowly over time with ***an average t<sub>2</sub>*** elimination half-life of 12.5 " 10 days. There was little increase or ***No*** accumulation in ***of total Pt-platinum was observed*** after multiple weekly treatments. ***After the first dose***, the ***peak*** appearance of free Pt ***concentration*** in plasma was reached at delayed from the time of administration with an average t<sub>max</sub> value of ***0.80"0.43 hours*** 45 min. The C<sub>max</sub> averaged ***103"50 ng/ml and decreased over time with a t<sub>2</sub> of 8.9"8.1 hours*** was variable, ranging from 15 to 229 ng/mL with an average of 95 ng/mL that fell below the

detection limits (5 ng/mL) after 4 hours. The peak free Pt levels in plasma were transient and much lower than the sustained exposure of 1.5 to 2.0 Fg/mL normally considered the lower threshold for nephrotoxicity. **Systemic exposure to free platinum as measured by** The estimated AUC ( $t_0$  to  $t_4$ ) for free Pt ranged from **204-4310 ngCh/mL** 0.2 to 4.3 FgCh/mL. **Systemic Apparent clearance and apparent volume of distribution of free platinum** averaged **632"758 573"155 mL/h/kg** and **3.7"2.1 L/kg, respectively.** the apparent volume of distribution during the elimination phase ( $V_z$ ) was 200 L for free Pt. These observations are consistent with local sequestration of Pt at the injection site and delayed release into the systemic circulation.

## (C) COMMENTS

### - TO THE FIRM

1. A considerably high variability is observed in all pharmacokinetic parameters for both total and free platinum following intratumor administration of IntraDose (%CV=34-176%) (Study #516). This variability could not be explained by differences in age, gender, and dose administered. Please explain what are the reasons for the high variability of cisplatin pharmacokinetics after IntraDose Administration?
2. It is noted that the median  $t_{max}$  values for total platinum after intratumoral administration of Intradose in Study #516 were comparable to that after intravenous administration of cisplatin Injection in Johnson's Study, 1.5 (0.08-24) hours versus 1.2 (1.0-1.4) hours, respectively. You have mentioned that when IntraDose gel is administered intratumorally, cisplatin is retained at or near the site of injection and its local decay into the systemic circulation is prolonged. Only a few patients had prolonged  $t_{max}$  value in the study supporting your hypothesis; 3/16 patients had a  $t_{max}$  value of 24 hours. In the remaining 13 patients  $t_{max}$  ranged from 0.08-6.0 hours, demonstrating a highly variable retention of cisplatin at the tumor site. Please explain why only few patients(3 out of 16) retained the drug at the site of injection after IntraDose administration as demonstrated by the prolonged  $T_{max}$  value of 24 hours for total platinum?

### - TO MEDICAL REVIEWER

3. The Applicant claims that maximum platinum plasma levels ( $C_{max}$ ) are much lower following IntraDose administration than that following intravenous cisplatin. Dose-normalized  $C_{max}$  (normalized to 1 mg/m<sup>2</sup> platinum dose) is significantly lower after intratumor administration of IntraDose than that after intravenous cisplatin, by about 1.6- and 2.8-fold lower for total and free platinum, respectively (Study 516). Exposure to IntraDose is comparable or even higher to that after intravenous cisplatin. Dose-normalized AUC<sub>0-4</sub> (normalized to 1 mg/m<sup>2</sup> platinum dose) after IntraDose administration is 1.8-fold higher for total platinum and 1.1-fold lower for free platinum than after intravenous cisplatin. These differences are not statistically significant.

4. It is noted from the pooled PK data from the three studies (Studies 516, 43, and Johnson's) following IntraDose administration that there is a trend for systemic clearance of both total and free platinum to decrease as age increases ( $CL=7.7-0.06 \times \text{Age}$ ,  $r=0.217$  and  $CL=935-9.7 \times \text{Age}$ ,  $r=0.285$ , respectively). Systemic clearance was comparable between male and female patients for total platinum [ $CL=4.2 \text{ ml/hr/m}^2$  and  $4.4 \text{ ml/hr/m}^2$ , respectively], but was 30% lower in female than male patients for free platinum [ $CL=255 \text{ ml/hr/m}^2$  (74%) versus  $377 \text{ ml/hr/m}^2$  (82%), respectively]. In addition, the kinetics of free platinum are dose-dependent and may accumulate more in elderly and female patients. A precaution statement may need to be added to the package insert for the use of IntraDose in elderly and female patients.
5. The results from Study 43 and Johnson's Study are irrelevant to this NDA submission. First, these studies did not validate the assay methods used for determination of total and free platinum in plasma samples. Secondly, the patient population (i.e., patients with hepatocellular carcinoma) enrolled in these studies is not the relevant population for which IntraDose is indicated (i.e., patients with SCCHN). Therefore, any Pharmacokinetic information obtained in these studies should not be included in the package insert for IntraDose.

**(D) Briefing on** , 2001: (Attendees: Drs.: )

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Team Leader: Atiqur Rahman, Ph.D.  
Division of Pharmaceutical Evaluation I

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Reviewer: Sophia Abraham, Ph.D.  
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cc: NDA: 21-236  
HFD-150/Division file  
HFD-150/Spillman, Williams, Frykman  
HFD-860/Mehta, Rahman, Abraham  
CDR/Biopharm

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## Appendix 1: Firm’s Proposed Package Insert

- Attachment 1: Firm’s Formulations
- Attachment 2: Firm’s Results for Study MP #516-99-PK
- Attachment 3: Firm’s Results for Study MP # 43-92-P-PK
- Attachment 4: Firm’s Results for Johnson’s Study
- Attachment 5: Firm’s Analytical Methodology and Validation

### III. LIST OF ABBREVIATIONS

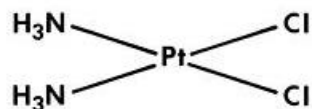
AUC <sub>0-4</sub>	Area under plasma concentration/time curve from time zero to infinity
CDDP	Cisplatin
C <sub>max</sub>	Peak plasma concentration
Cm <sup>2</sup>	Squared centimeter
Cm <sup>3</sup>	Cubic centimeter
CL	Systemic Clearance
%CV	Coefficient of variation [%CV=(standard deviation/mean) x 100]
Epi	Epinephrine
HC	Hepatocellular carcinoma
hr	Hour
IV	Intravenous
MRT	Mean residence time
NDA	New Drug Application
PDR®	Physician's Desk Reference®
PK	Pharmacokinetics
Pt	Platinum
SCCHN	Squamous cell carcinoma of the head and neck
t <sub>max</sub>	Time to reach C <sub>max</sub>
t <sub>2</sub>	Elimination half-life
V <sub>z</sub>	Apparent volume of distribution

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### IV. BACKGROUND

IntraDose (cisplatin/epinephrine, CDDP/epi) Injectable Gel is a novel drug delivery system intended for intratumoral administration. IntraDose contains the antineoplastic agent, cisplatin (CDDP), and the local vasoconstrictor, epinephrine (epi), in a viscous biodegradable aqueous matrix of purified bovine collagen. Epinephrine and collagen both help to limit the spread of cisplatin outside of the site of injection.

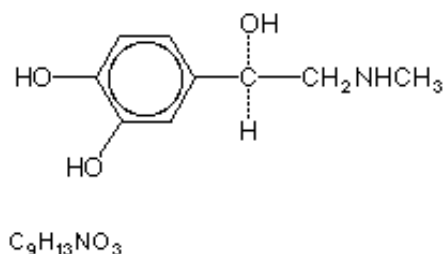
Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position.



Cisplatin, an alkylating agent, binds intracellularly with DNA, RNA, or other macromolecules at two sites to form interstrand and intrastrand links. These intrastrand links account for > 90% of the platinum binding to DNA. Cisplatin causes cell cycle arrest in the G<sub>2</sub>-phase and then induces programmed cell death or apoptosis. The

recommended cisplatin doses are 50-70 mg/m<sup>2</sup> IV per cycle once every 3 to 4 weeks as a single agent for the treatment of advanced bladder cancer, 20 mg/m<sup>2</sup> IV daily for 5 days per cycle in combination with other approved chemotherapeutic agents for the treatment of testicular cancer, and 75-100 mg/m<sup>2</sup> IV per cycle once every 4 weeks in combination with cyclophosphamide for the treatment of metastatic ovarian tumors (PDR®).

Epinephrine is an endogenous sympathomimetic catecholamine that has many therapeutic applications.



Endogenous epinephrine is produced primarily from norepinephrine in the adrenal medulla. Epinephrine can be administered by injection, inhalation, or administered topically to the eye; the effects of exogenous epinephrine are identical to those of the endogenous hormone. Epinephrine is administered subcutaneously (SC), intramuscularly (IM), or intravenously (IV) at recommended doses of 0.3-0.5 mg SC, 0.3-0.5 mg IM, or 0.1-0.25 mg IV (PDR®).

The proposed indication in the present NDA submission is the use of CDDP/epi gel in the treatment of patients with recurrent squamous cell carcinoma of the head and neck (SCCHN) whose tumors considered incurable with surgery or radiotherapy. The CDDP/epi gel is prepared immediately prior to use from sterile and nonpyrogenic components supplied in kit form. The kit includes a vial of IntraPlatinJ (CDDP Injectable suspension, 11 mg), a vial of IntraEpiJ (epi solution, 0.152 mg/ml), and a syringe of IntraGeU (aqueous collagen gel, 6.5%). Each kit will provide 2 ml of IntraDose after mixing. Each 1-ml of IntraDose contains 4-mg cisplatin, 0.1-mg epinephrine, and 20-mg purified bovine collagen (see Attachment 1 for details).

## V. QUESTION-BASED REVIEW

**!      *What is the rationale for the proposed dosing regimen provided in the NDA?***

No attempt was made to correlate exposure to IntraDose and response rate. The proposed dosing schedule of 0.25 ml IntraDose per cm<sup>3</sup> of tumor volume administered weekly (one cycle) was selected on the basis of clinical experience. The 0.25 ml dose per cm<sup>3</sup> of tumor volume in Phase III studies showed optimum risk/benefit ratio for

patients. The weekly administration of IntraDose in earlier trials was both tolerable and feasible for the routine management of patients with advanced head and neck cancer.

***! Has the Applicant adequately characterized the pharmacokinetics (PK) of total and free Platinum from IntraDose in the target population (i.e., head and neck cancer patients)?***

Study MP #516-99-PK assessed the pharmacokinetics (PK) of total and free platinum (Pt) in patients with head and neck cancer following intratumoral administration of IntraDose. The report of this study was included in the 4-month Safety Update for IntraDose in the Submission of May 2, 2001.

The Human Pharmacokinetics and Bioavailability section of the NDA submission (Submission of January 2, 2001) included two other studies which also assessed the PK of total and free platinum but in patients with advanced **liver cancer**. One study was sponsored by Matrix Pharmaceuticals as part of an early phase II study (Study MP #43-92-P-PK) and the other was conducted independently by one of the investigators (Dr. Philip Johnson) in some of his patients in the Matrix Study No. 417-96-2.

M Study MP #516-99-PK, entitled “Open-Label Study to Determine Total and Unbound Plasma Platinum Levels in Patients Receiving Cisplatin/Epinephrine (CDDP/epi) Injectable Gel Intratumorally for Recurrent or Refractory Squamous Cell Carcinoma of the Head and Neck”.

M Study MP #43-92-P-PK, entitled “Phase I Trial of Intralesional CDDP-e Therapeutic Implant in Patients with Primary or Metastatic Cancer of the liver”.

M Johnson’s Study, entitled “Pharmacokinetic Study of Intralesional Cisplatin/Epinephrine Injectable Gel in Hepatocellular Carcinoma”.

**Study MP #516-99-PK** evaluated the PK of total and free platinum (Pt) in 16 patients with SCCHN (13 males/3 females, 40-67 years of age). Patients were treated by direct intratumor injection of 2.6-6.4 ml of IntraDose gel (depending on tumor size) every week for 6 weeks. CDDP doses from the gel ranged from 12-25.6 mg (6.8-16.4 mg/m<sup>2</sup>). Plasma samples were collected pre-dose and at 0.08, 0.33, 0.67, 1, 2, 4, 4.5, 24, and 48 hours after the first dose in all patients and also after the third dose in six of 16 patients. Total as well as free Pt plasma levels were determined by atomic absorption spectrophotometry. The assay was adequately validated. Calibration curves were linear over the concentration range of 150-5000 ng/ml for total Pt and 30-600 ng/ml for free Pt. The lower limit of quantitation was 150 ng/ml for total Pt and 30 ng/ml for free Pt. Intra- and inter-day assay precision, as expressed by percent relative standard deviation (%RSD), was less than 10% for quality control data for both total and free Pt. Separation of free Pt fraction was carried out by ultrafiltration. The formulation gel for marketing was used in this study (see Attachment 1). Results of this study are

presented in Attachment 2. The assay methodology and validation are presented in Attachment 5.

**Study MP #43-92-P-PK** evaluated the PK of total and free platinum in eight patients (4 males/4 females, 37-75 years of age). Of the eight patients, two had hepatocellular carcinoma and the six others had a variety of tumor types (colorectal adenocarcinoma, pancreatic, gall bladder adenocarcinoma, small bowel leiomyosarcoma, and gastric leiomyosarcoma) metastatic to the liver. The volume of IntraDose administered ranged from 4.8-25 ml depending on tumor size. The gel was administered intralesionally by ultrasound-guided injection every other week for 8 weeks. CDDP doses from the gel ranged from 19-100 mg (10-63 mg/m<sup>2</sup>). Plasma samples were collected pre-dose and at 0.08, 0.33, 0.67, 1, 2, 6, 24, 48, 72, and 96 hours after first dose in all patients and also after second dose in four of eight patients. Six-hour urine samples were collected from 7 of 8 patients. Total as well as unbound platinum levels in plasma and total platinum levels in urine were determined by atomic absorption spectrophotometry (NOT validated, Submission of April 25, 2001). Separation of free Pt fraction was carried out by precipitation. A prototype CDDP/epi gel formulation was used in this study (see Attachment 1). Results of this study are presented in Attachment 3.

**In Johnson's Study**, the PK of total and unbound platinum were assessed after intralesional injection of CDDP/epi gel or after intravenous infusion of CDDP in cirrhotic patients with unresectable hepatocellular carcinoma. Six patients (4 males/2 females, 48-75 years of age) received 2.5-10 ml CDDP/epi gel weekly or biweekly over 6-week period. CDDP doses from the gel ranged from 10-40 mg (6-23 mg/m<sup>2</sup>). For comparison, another four male patients (52-68 years of age) received 100 mg (75 mg/m<sup>2</sup>) CDDP intravenously (IV) over 1-hour infusion. Plasma samples were collected pre-dose and at 0.083, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 21, 24, 48, 72, 168, and 336 hours from patients receiving the CDDP/epi gel and pre-dose and at 0.083, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 21, 24, 48, 72, 96, 168, and 384 hours from patients receiving the CDDP infusion. Urine samples were collected to 336 hours from patients receiving the CDDP/epi gel post-infusion and up to 148 hours from patients receiving the CDDP infusion. Total as well as unbound platinum levels in plasma and total platinum levels in urine were determined by atomic absorption spectrophotometry (NOT validated, Submission of April 25, 2001). Separation of unbound platinum fraction was carried out by ultrafiltration. The formulation gel for marketing was used in this study (see Attachment 1). Results of this study are presented in Attachment 4.

**Note:** In the studies submitted, no attempt was made to compare the PK parameters of CDDP in the presence or absence of epinephrine (epi) after intratumor administration. However, no drug interaction is expected to occur between CDDP and epinephrine since both drugs have different metabolic pathways. Epinephrine is rapidly and extensively metabolized by the enzymes, catechol-O-methyltransferase and monoamine oxidase, in the liver and in other tissues to inactive metabolites. Cisplatin, due to its unique chemical structure, its chlorine atoms are more subject to chemical

displacement reactions by nucleophiles, such as water or sulfahydryl groups, than to enzyme-catalyzed metabolism.

### **Overall Results:**

The overall results from the above PK studies are reported in Table 1 as mean (%CV) PK parameters for total and free Pt after the first dose (Cycle 1). Table 2 (a and b) shows the effect of treatment cycle, as measured by comparing dose-normalized  $C_{\max}$  and  $AUC_{0-4}$  values between the first and third dose in Study 516 (n=4) and in Johnson's Study (n=5) and between the first and second dose in Study 43 (n=4). Table 3 shows the effect of tumor type (SCCHN versus HC) on dose-normalized  $C_{\max}$  and  $AUC_{0-4}$  following the first cycle of IntraDose treatment. Figures 1-5 show various analyses made on overall data set.

**Table 1. Mean (%CV) PK Parameters After the First Dose**

Study #	MP #516-99-PK		MP #43-92-P-PK		Johnson's Study			
No. of Patients	16		8		6		4	
Route of Administration	Intratumor		Intralesional		Intralesional		1-Hour Infusion	
Dosage Form	IntraDose <sup>o</sup>		IntraDose <sup>x</sup>		IntraDose <sup>o</sup>		Cisplatin Solution	
Tumor Type	SCCHN		HC		HC		HC	
Tumor size	10.5-25.5 cm <sup>3</sup>		37-3164 cm <sup>3</sup>		*NR		--	
Volume of IntraDose administered	2.6-6.4 ml		4.8-25 ml		2.5-10 ml		--	
CDDP Dose (mean, range)	10 mg/m <sup>2</sup> 6.8-16.4 mg/m <sup>2</sup>		45 mg/m <sup>2</sup> 10-63 mg/m <sup>2</sup>		Table 0. mg/m <sup>2</sup> 6-23 mg/m <sup>2</sup>		76.6 mg/m <sup>2</sup> 75.1-77.4 mg/m <sup>2</sup>	
Pt Dose (mean, range)	6.8 mg/m <sup>2</sup> 4.4-10.7 mg/m <sup>2</sup>		29.2 mg/m <sup>2</sup> 6.5-38.2 mg/m <sup>2</sup>		10.5 mg/m <sup>2</sup> 3.9-15.2 mg/m <sup>2</sup>		49.8 mg/m <sup>2</sup> 48.8-50.3 mg/m <sup>2</sup>	
Mean (%CV) PK Parameter	Total Pt	Free Pt	Total Pt	Free Pt	Total Pt	Free Pt <sup>§</sup>	Total Pt	Free Pt
C <sub>max</sub> (ng/ml)	250 (34%)	103 (49%)	781 (65%)	472 (83%)	465 (43%)	345 (62%)	3130 (15%)	2210 (21%)
<sup>c</sup> C <sub>max</sub> /Dose (ng/ml/mg/m <sup>2</sup> )	38.7 (42%)	15.7 (42%)	27 (65%)	19.8 (83%)	46 (24%)	32 (62%)	62.9 (16%)	44 (21%)
<sup>s</sup> p-value (T-test)	0.0038	0.0029	0.0007	0.0046	0.0236	0.165	--	--
<sup>&amp;</sup> t <sub>max</sub> (hr)	1.5 (0.08-24)	0.67 (0.08-1)	6.0 (0.33-24)	0.66 (0.33-1)	0.825 (0.43-48)	0.65 (0.26-0.83)	1.2 (1-1.4)	1.2 (1-1.4)
AUC <sub>0-4</sub> (ng.hr/ml)	71687 (102%)	823 (136%)	234200 (147%)	5313 (73%)	78483 (83%)	1705 (114%)	338650 (21%)	7760 (27)
<sup>c</sup> AUC <sub>0-4</sub> /Dose (ng.hr/ml/mg/m <sup>2</sup> )	11453 (108%)	118 (115%)	7650 (120%)	178 (61%)	7276 (75%)	134 (87%)	6817 (23%)	156 (29%)
<sup>s</sup> p-value (T-test)	0.061	0.186	0.405	0.317	0.427	0.376	--	--
CL (ml/hr/kg)	4.1 (80%)	632 (120%)	7.4 (95%)	217 (73%)	4.7 (38%)	386 (100%)	4.03 (16%)	180 (48%)
V <sub>z</sub> (L/kg)	1.05 (55%)	3.7 (59%)	1.3 (43%)	18.7 (55%)	1.06 (37%)	15.2 (23%)	1.1 (13%)	11.4 (45%)
MRT (hr)	376 (74%)	17.5 (147%)	482 (167%)	143 (109%)	250 (54%)	56.2 (109%)	281 (9.6%)	38 (53%)
t <sub>1/2</sub> (days)	299 (81%)	8.9 (91%)	334 (167%)	108 (103%)	176 (53%)	52.2 (94%)	193 (14%)	45.0 (46%)
% of Total Pt dose excreted in urine	<sup>#</sup> ND	<sup>#</sup> ND	3.7% (58%)	<sup>#</sup> ND	4.25% (14%)	<sup>#</sup> ND	33% (13%)	<sup>#</sup> ND

<sup>o</sup> Commercial formulation

<sup>x</sup> Prototype formulation

\*NR (Not Reported)

<sup>&</sup> Median (range)

<sup>§</sup> Data are available from 4 patients

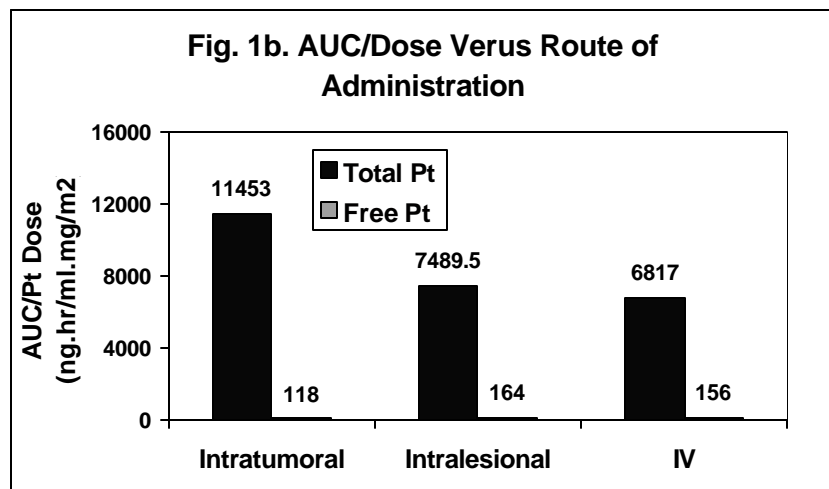
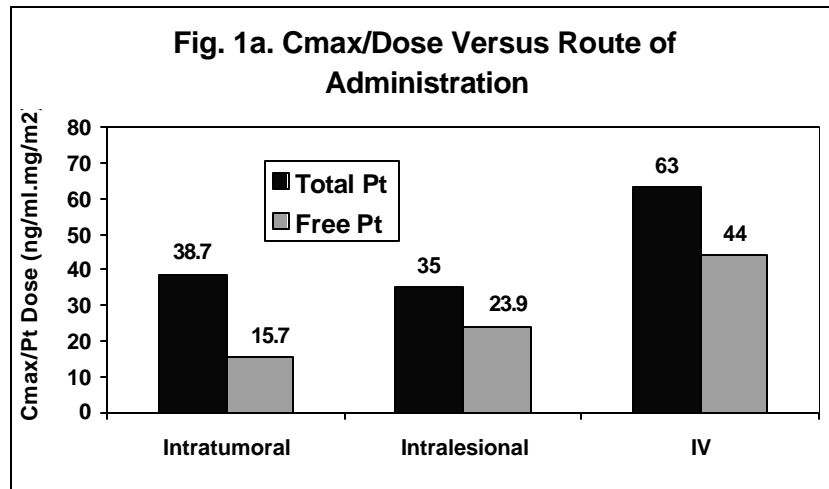
<sup>c</sup> Normalized to 1-mg/m<sup>2</sup> Pt dose

<sup>s</sup> T-Test for 1-tailed distribution and two samples with unequal variance for IntraDose compared to IV cisplatin

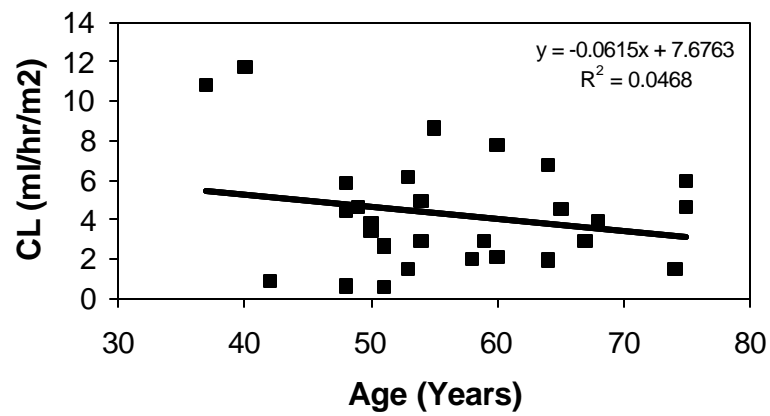
<sup>#</sup> ND (Not Determined)

<sup>·</sup> Over the first 6 hours

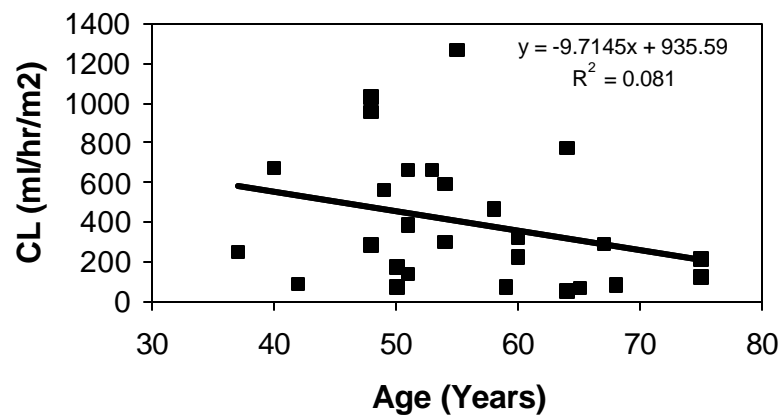
<sup>'</sup> Over 72 hours



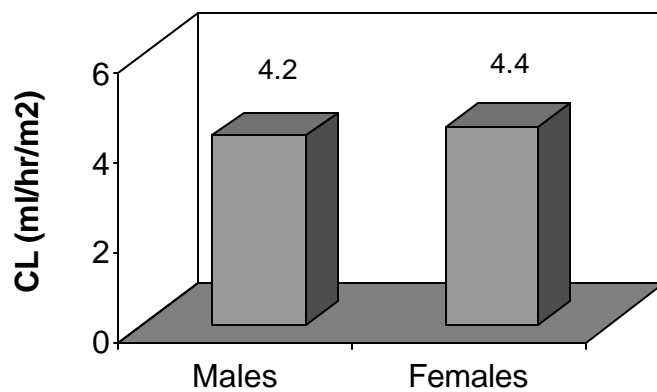
**Fig. 2a. CL Versus Age for Total Pt After IntraDose Administration**



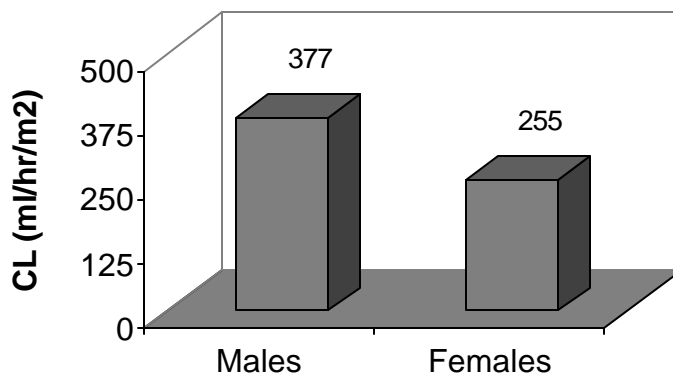
**Fig. 2b. CL Versus Age for Free Pt After IntraDose Administration**

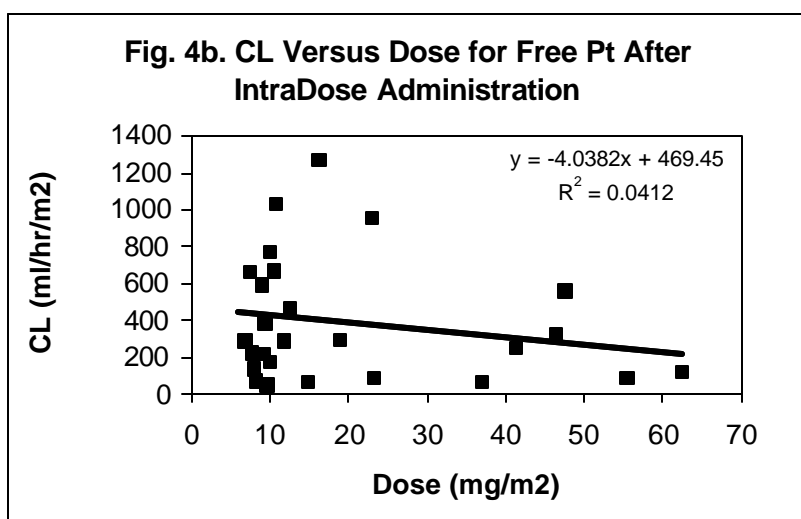
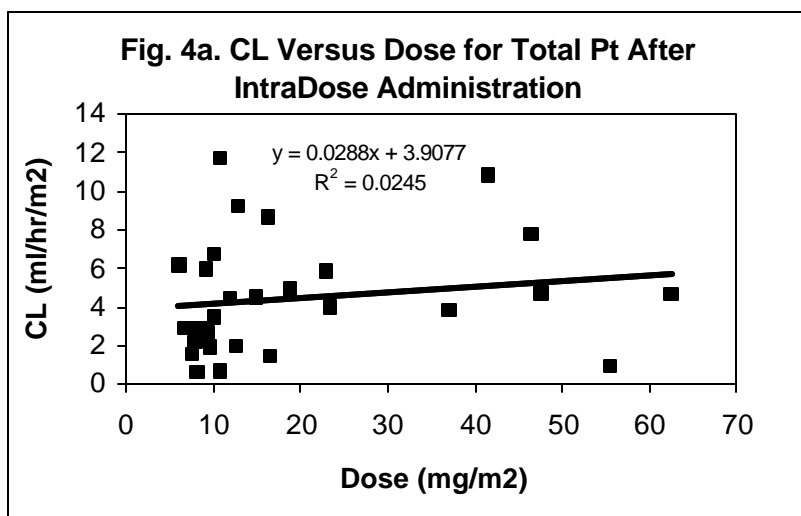


**Fig. 3a. CL Versus Gender for Total Pt After IntraDose Administration**

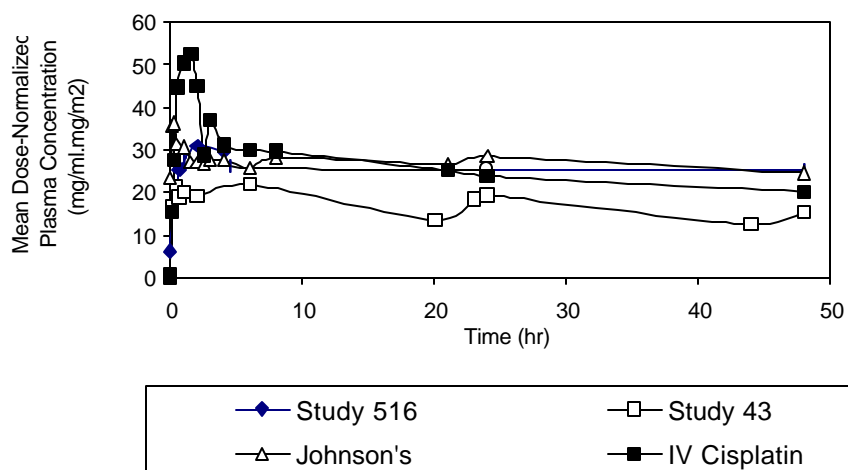


**Fig. 3b. CL Versus Gender for Free Pt After IntraDose Administration**

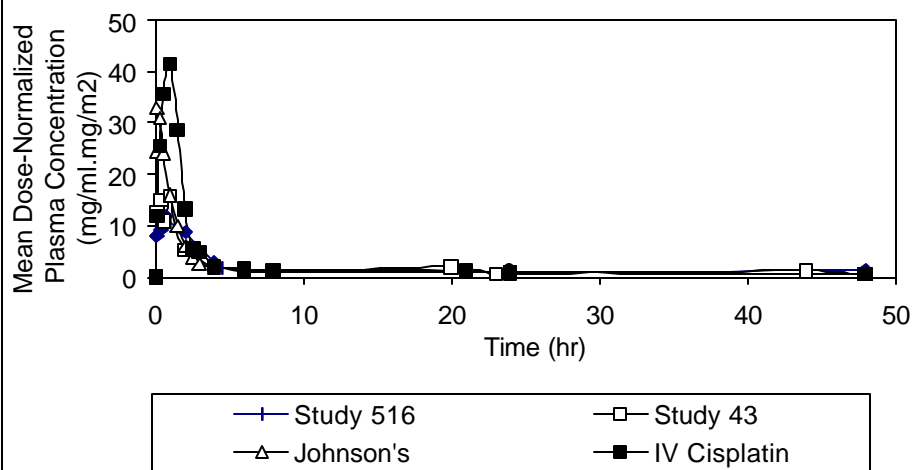




**Fig. 5a. Mean Plasma Cocentration/Time Profile  
for Total Platinum**



**Fig. 5b. Mean Plasma Cocentration/Time Profile  
for Free Platinum**



**Table 2a. Effect of Treatment Cycle (For Total Pt)**

PK Parameter	Total Pt					
	Study 516 (n=4)		Study 43 (n=4)		Johnson's Study (n=5)	
Cycle #	1 <sup>st</sup>	3 <sup>rd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	3 <sup>rd</sup>
Pt Dose (mg/m <sup>2</sup> )	5.5 (4.4-6.2)	5.5 (4.4-6.2)	31.9 (24-40.6)	29.8 (7.2-57.8)	9.5 (3.9-14.9)	10.4 (4.7-14.9)
C <sub>max</sub> (ng/ml)	275 (33%)	257 (34%)	1150 (39%)	1147 (82%)	396 (30%)	400 (41%)
C <sub>max</sub> /Pt Dose (ng/ml.mg/m <sup>2</sup> )	49.01 (26%)	46.1 (27%)	38.5 (50%)	39.1 (29%)	45.1 (27%)	41.4 (38%)
*p-value	0.377		0.480		0.355	
AUC <sub>0-4</sub> (ng.hr/ml)	94875 (112%)	126800 (70%)	381950 (122%)	162625 (28%)	74820 (111%)	146220 (38%)
AUC <sub>0-4</sub> /Pt Dose (ng.hr/ml.mg/m <sup>2</sup> )	16162 (103%)	23014 (73%)	11095 (113%)	10627 (90%)	7474 (91%)	12651 (32%)
*p-value	0.292		0.477		0.132	

\*T-Test for 1-tailed distribution and two samples with unequal variance

**Table 2b. Effect of Treatment Cycle (For Free Pt)**

PK Parameter	Free Pt					
	Study 516 (n=4)		Study 43 (n=4)		Johnson's Study (n=3)	
Cycle #	1 <sup>st</sup>	3 <sup>rd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	1 <sup>st</sup>	3 <sup>rd</sup>
Pt Dose (mg/m <sup>2</sup> )	5.5 (4.4-6.2)	5.5 (4.4-6.2)	31.9 (24-40.6)	29.8 (7.2-57.8)	11.03 (5.9-14.9)	12.3 (8.2-14.9)
C <sub>max</sub> (ng/ml)	120 (32%)	60 (83%)	735 (56%)	640 (145%)	253 (52%)	437 (107%)
C <sub>max</sub> /Pt Dose (ng/ml.mg/m <sup>2</sup> )	21.6 (21%)	10.6 (74%)	24.5 (64%)	14.3 (96%)	29.5 (80%)	37.2 (90%)
*p-value	0.031		0.178		0.383	
AUC <sub>0-4</sub> (ng.hr/ml)	1183 (93%)	691 (86%)	80485 (129%)	3207 (88%)	736 (46%)	763 (75%)
AUC <sub>0-4</sub> /Pt Dose (ng.hr/ml.mg/m <sup>2</sup> )	205 (83%)	120 (77%)	2251 (113%)	110 (48%)	79 (59%)	68 (73%)
*p-value	0.211		0.095		0.407	

\*T-Test for 1-tailed distribution and two samples with unequal variance

**Table 3. Effect of Tumor Type**

PK Parameter	Total Pt		Free Pt	
	SCCHN	HC <sup>#</sup>	SCCHN	HC <sup>#</sup>
N	16	14	16	12
C <sub>max</sub> /Pt Dose (ng/ml.mg/m <sup>2</sup> )	38.7	35.3	15.7	23.9
p-value*	0.293		0.075	
AUC <sub>0-4</sub> /Pt Dose (ng.hr/ml.mg/m <sup>2</sup> )	11453	7488	118	164
p-value*	0.112		0.169	

\*T-Test for 1-tailed distribution and two samples with unequal variance for IntraDose after the first dose

<sup>#</sup>Data from Study #43 and Johnson's Study were combined.

From the Tables and Figures above, it is noted that:

- A considerably high variability is observed in all PK parameters for both total and free Pt following IntraDose administration (either intratumor or intralesional) (%CV=34-176%). This variability could not be explained by differences in age, gender, and dose administered. Analysis of pooled data from the three studies following IntraDose administration (n=30, 21 males, 9 females) shows that there is a trend for systemic clearance for both total and free Pt to decrease as age increases (Figures 2a and 2b). Male and female patients have comparable systemic clearance for total Pt, CL=4.2 ml/hr/m<sup>2</sup> (62%) and 4.4 ml/hr/m<sup>2</sup> (82%), respectively. For free Pt, systemic clearance is 30% lower in female patients than in male patients [CL=255 ml/hr/m<sup>2</sup> (74%) versus 377 ml/hr/m<sup>2</sup> (82%), respectively] (Figures 3a and 3b). Nonlinearity is observed in the kinetics of free Pt (Fig. 4a and 4b); this is also reported in PDR®. Variability following the 1-hour IV cisplatin infusion (Johnson's Study) is much lower, and is lower for total Pt (%CV=9.6-23%) than free Pt (%CV=21-53%).
- The median t<sub>max</sub> values for total Pt are 1.5 hours, 6 hours, and 0.825 hours in Studies 516, 43, and Johnson's, respectively, compared to 1.2 hours after IV cisplatin infusion. The Applicant claims that when IntraDose gel is administered intratumorally, the drug is retained at or near the site of injection and its availability to the systemic circulation is prolonged. Only few patients had shown to have a prolonged t<sub>max</sub> value for total Pt; 3/16 patients in Study 516 had a t<sub>max</sub> value of 24 hours, 2/8 patients in Study 43 had t<sub>max</sub> values of 24 and 20 hours, and 2/6 patients in Johnson's Study had t<sub>max</sub> values of 23.7 and 48 hours. This demonstrates highly variable retention of cisplatin at the tumor site.
- Dose-normalized C<sub>max</sub> (normalized to 1 mg/m<sup>2</sup> Pt dose) following IntraDose administration is significantly lower than that after the 1-hour IV cisplatin infusion for both total and free Pt (p < 0.05, Table 1). For total Pt, dose-normalized C<sub>max</sub> is about 1.6-, 2.3- and 1.4-fold lower after IntraDose than IV

cisplatin in Studies 516, 43, Johnson's, respectively; the corresponding values for free Pt are 2.8-, 2.2- and 1.3-fold lower, respectively.

- Exposure to IntraDose, as expressed by dose-normalized  $AUC_{0-4}$  (normalized to 1 mg/m<sup>2</sup> Pt dose), is not significantly different from that after IV cisplatin for both total and free Pt ( $p > 0.05$ , Table 1). Dose-normalized  $AUC_{0-4}$  values for total and free Pt after IntraDose administration are comparable to that after IV cisplatin administration, except in Study 516, dose-normalized  $AUC_{0-4}$  it for total Pt after IntraDose administration is 1.8-fold higher than that after cisplatin IV administration.
- Figures 5a and 5b show that mean dose-normalized plasma concentration/time profiles for total and free Pt are comparable after intraDose and IV cisplatin administrations. These profiles are even superimposable for free Pt, the pharmacologically active species of cisplatin.
- For both total and free Pt, no significant differences are observed in dose-normalized  $C_{max}$  and  $AUC_{0-4}$  either between the first and second dose in Study 43 or between the first and third dose in Study 516 and Johnson's Study ( $p > 0.05$ , Table 2, a and b). The difference observed in  $C_{max}/dose$  for free Pt in Study 516 ( $p=0.031$ ) may be due an artifact. This means that total and free Pt do not accumulate upon weekly administration of IntraDose. However, this contradicts with the mean  $t_2$  value of 299, 334, 176 hours for total Pt (12.5, 14, 7.3 days, Table 1) at which accumulation of total pt is expected upon weekly administration of IntraDose. The  $t_2$  may be overestimated.
- Finally, tumor type has not effect on in dose-normalized  $C_{max}$  and  $AUC_{0-4}$  for both total and free Pt following IntraDose administration ( $p > 0.05$ , Table 3).

In conclusion, the data submitted are considerably variable. The results demonstrated that IntraDose as a novel drug delivery system did not appear to achieve the goal of targeting cisplatin directly into tumor tissues with much slower rate of appearance of platinum in systemic circulation. Although dose-normalized  $C_{max}$  for both total and free Pt was significantly lower after IntraDose than after IV cisplatin, exposure to both moieties was comparable between the two treatments. Mean dose-normalized plasma concentration/time profiles for free platinum (the pharmacologically active species for cisplatin) are superimposable after IntraDose and IV cisplatin administrations. No accumulation of platinum occurred upon weekly administration of IntraDose. Tumor has no effect on PK parameters of both total and free platinum.

## APPENDIX 1

Labeling Text	NDA Cross Reference Volume/Page
<b>Rx only</b>	
<p><b>DESCRIPTION</b></p> <p>IntraDose<sup>®</sup> (cisplatin/epinephrine) Injectable Gel is a viscous, opaque, pale yellow gel containing the antineoplastic agent, cisplatin, and the vasoconstrictor, epinephrine, in an aqueous matrix of purified bovine collagen. It is intended only for intratumoral administration. The drug product is provided as a single-use kit containing one single-use vial of IntraPlatin<sup>™</sup> (cisplatin for injectable suspension), one single-use vial of IntraEpi<sup>™</sup> (epinephrine solution, 0.152 mg/mL), and one single-use syringe of IntraGel<sup>™</sup> (6.5% collagen gel). The product is prepared shortly before use. Each kit will provide 2 mL of IntraDose after mixing.</p>	Vol. 2.1/pg. 57
<p>When prepared as directed, 1 mL of IntraDose contains: cisplatin (4 mg), epinephrine (0.1 mg), mannitol (40 mg), sodium chloride (37 mg), purified bovine collagen (20 mg), sodium phosphate dibasic (2.1 mg), sodium phosphate monobasic (1.8 mg), polysorbate 80 (0.7 mg), acetic acid (0.3 mg), sodium metabisulfite (0.1 mg), sodium acetate (0.1 mg) and edetate disodium (0.07 mg). The pH of the mixed gel is approximately 6.2.</p>	Vol. 2.1/pg. 59

Labeling Text	NDA Cross Reference Volume/Page
<p><u>Kit Components</u></p> <p>Each vial of IntraPlatin contains 11 mg cisplatin formulated with mannitol (110 mg) and sodium chloride (99 mg) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may be added during manufacture to adjust pH.</p>	Vol. 2.1/pg. 60
<p>IntraEpi is a sterile aqueous solution containing epinephrine (0.152 mg/mL), polysorbate 80 (1 mg/mL), glacial acetic acid (0.49 mg/mL), sodium metabisulfite (0.2 mg/mL), sodium acetate (0.15 mg/mL), and edetate disodium dihydrate (0.1 mg/mL). Hydrochloric acid and/or sodium hydroxide may be added during manufacture to adjust pH. IntraEpi differs significantly from other commercial preparations of epinephrine and is specifically designed for IntraDose preparation.</p>	Vol. 2.1/pg. 60
<p>IntraGel is a sterile aqueous collagen gel formulation containing purified bovine collagen (65 mg/g); dibasic sodium phosphate, heptahydrate (17.9 mg/g); monobasic sodium phosphate, monohydrate (4.6 mg/g); and sodium chloride (2.6 mg/g).</p>	Vol. 2.1/pg. 61
<p><u>Active Ingredients</u></p> <p>Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position, and has the molecular formula <math>\text{Cl}_2\text{H}_6\text{N}_2\text{Pt}</math> and a molecular weight of 300.1. It exists as a yellow to yellow-orange microcrystalline powder or crystals. It is slightly soluble in water, sparingly soluble in dimethyl formamide, practically insoluble in ethanol. It has the following structure:</p> <div data-bbox="565 1493 768 1646" data-label="Chemical-Block"> <pre>       Cl   NH3        \   /         Pt        /   \       Cl   NH3           </pre> </div>	Vol. 2.1/pg. 52
<p>Epinephrine is (R)-4-[1-hydroxy-2-(methylamino)ethyl]-1,2-benzenediol, <math>\text{C}_9\text{H}_{13}\text{NO}_3</math> (molecular weight of 183.21). Epinephrine as the free base is</p>	Vol. 2.1/pg. 54

Labeling Text	NDA Cross Reference Volume/Page
<p>very slightly soluble in water and in alcohol. Epinephrine is freely soluble in water at neutral or acid pH. It has the following structure:</p> <div data-bbox="560 401 776 667" data-label="Chemical-Block"> <chem>CNCC(O)c1cc(O)ccc1O</chem> </div>	
<p><b>CLINICAL PHARMACOLOGY</b></p> <p>Cisplatin is a cytotoxic agent with a long history of use in treating solid tumors when administered intravenously. Although its mechanism of action is not fully understood, it is believed to form inter- and intrastrand DNA crosslinks which interfere with DNA function, inducing cell death through the apoptotic cascade. Cisplatin also forms DNA-protein crosslinks and interacts with other cell components, such as glutathione. Epinephrine is a well-known catecholamine, active at <math>\alpha</math>- and <math>\beta</math>-receptors. One of its pharmacological activities is to cause arteriolar vasoconstriction. IntraDose is designed to provide local delivery and retention of cisplatin within solid tumors by direct intratumoral injection, achieving much higher local concentrations of the drug within the tumor and for longer periods of time than can be achieved with either systemic or local administration of cisplatin solutions. The epinephrine is believed to aid tumor retention of the cisplatin by restricting local blood flow.</p>	<p>Vol. 1.1/pg.47</p> <p>Vol. 1.1/pg. 48</p> <p>Vol. 1.1/pg. 119</p> <p>Vol. 1.1/pg. 67</p>
<p>In a pharmacokinetic study of IntraDose administered intratumorally to sixteen subjects (total of 20 treatments) with squamous cell carcinoma of the head and neck, platinum levels were monitored in plasma (total Pt), and plasma ultrafiltrate (free Pt). Patients received 0.25 mL gel/cm<sup>3</sup> of tumor volume, corresponding to cisplatin doses of 10.5 to 25.6 mg, averaging approximately 10 mg/m<sup>2</sup> body surface area. The maximum average total Pt concentration in the plasma (t<sub>max</sub>) was observed at 9.8 hours. Over this</p>	<p>Study 516-99-PK Vol. 5.4/pg. 1</p>

Labeling Text	NDA Cross Reference Volume/Page
<p>dose range, average observed total Pt peak plasma concentration (<math>C_{max}</math>) was 252 ng/mL and decreased slowly over time with a <math>t_{1/2}</math> of 12.5 days. There was little increase or accumulation in total Pt after multiple weekly treatments. The appearance of free Pt in plasma was delayed from the time of administration with an average <math>t_{max}</math> of 45 min. The <math>C_{max}</math> was variable, ranging from 15 to 229 ng/mL with an average of 95 ng/mL that fell below the detection limits (5 ng/mL) after 4 hours. The peak free Pt levels in plasma were transient and much lower than the sustained exposure of 1.5 to 2.0 <math>\mu</math>g/mL normally considered the lower threshold for nephrotoxicity. The estimated AUC (<math>t_0</math> to <math>t_{\infty}</math>) for free Pt ranged from 0.2 to 4.3 <math>\mu</math>g•h/mL. Systemic clearance of free Pt was <math>573 \pm 155</math> mL/h/kg and the apparent volume of distribution during the elimination phase (<math>V_z</math>) was 200 L for free Pt. These observations are consistent with local sequestration of Pt at the injection site and delayed release into the systemic circulation.</p>	
<p>In studies in tumor-bearing mice, intratumoral administration of IntraDose resulted in tumor platinum concentrations 40 to 80 times higher, and kidney levels three times lower, than were observed after intravenous administration of similar doses of cisplatin. Platinum levels in tumors after intratumoral injection of IntraDose remained in excess of 15 <math>\mu</math>g/g (approximately 75 <math>\mu</math>M) for up to 6 days after injection.</p>	<p>Study TB-1616 Vol. 4.5/pg. 55</p>

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<p><b>CLINICAL STUDIES</b></p> <p>A total of 396 patients with a variety of solid tumors have been treated in IntraDose clinical studies. The widest experience with IntraDose is in the treatment of squamous cell carcinoma of the head and neck (SCCHN), metastatic breast cancer, malignant melanoma and esophageal cancer. The clinical development program for SCCHN included two prospective, randomized, placebo-controlled studies in patients with recurrent or refractory SCCHN and two open-label, single-arm studies in patients with metastatic or recurrent tumors from a variety of primary sites.</p>	<p>ISS Section 1.3 Vo1. 4.13/ pg. 245 Study 414-93-2 Vol. 4.15/ pg. 1 Study 514-94-2 Vol. 4.42/ pg. 1 Study 403-93-2 Vol. 4.77/ pg. 1 Study 503-93-2 Vol. 4.100/pg. 1 Study 39-92-P Vol. 4.66/pg. 1</p>
<p><b>Head and Neck Cancer</b></p> <p>Two prospective, randomized, multicenter, double-blind, placebo-controlled studies support the use of IntraDose in the treatment of SCCHN. A total of 178 patients with tumors up to 20.0 cm<sup>3</sup> were enrolled and randomized 2:1 to receive IntraDose or placebo. The primary endpoints were objective response of a target tumor and the attainment of clinical benefit.</p>	<p><b>ISE Section 3.1.2.1 Vol. 4.13/pg. 130</b></p> <p><b>ISE Section 3.1.2.2 Vol. 4.13/pg. 135</b></p>
<p>One study enrolled and treated 86 patients in North America (62 IntraDose, 24 placebo); the second study enrolled and treated 92 patients in Europe (57 IntraDose, 35 placebo). Most patients (99%) were previously treated for their head and neck cancer; most (89%) had been heavily pretreated with multiple prior treatment modalities including surgery, radiotherapy and/or chemotherapy. Most tumors were located in the cervical, oral, facial or laryngopharyngeal regions. The treatment regimen consisted of up to 6 weekly injections of IntraDose or placebo (collagen gel only) within 8 weeks to one or more tumors. The dose administered in these studies was 0.25-0.5 mL/cm<sup>3</sup>.</p>	<p><b>ISE Section 3.1.3.2.2 Vol. 4.13/pg. 136</b></p> <p><b>ISE Section 3.1.2.1 Vol. 4.13/pg. 130</b></p>
<p><u>Target Tumor</u></p> <p>In the two controlled studies conducted in North America and Europe, patients could receive IntraDose treatment to more than one tumor.</p>	<p>ISE Section 3.1.2.1 Vol. 4.13/pg. 130</p>

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<p>However, a single target tumor was selected as a measure of objective tumor response. The target tumor was defined as the single most symptomatic, threatening or distressful to the patient or the largest tumor if a single tumor could not be identified as the most troublesome. The difference in response rate between IntraDose- and placebo-treated patients was statistically significant. This positive response to IntraDose treatment was demonstrated in patients who were heavily pretreated with multiple prior therapies and who had a low expectation of response to further treatment. These data are shown in the following table:</p>																																																																											
<p><b><i>Response of Target Tumor (Blinded Phase)</i></b></p> <table><tr><th rowspan="2">Placebo</th><th colspan="2">North America</th><th colspan="2">Europe</th></tr><tr><th>IntraDose</th><th>Placebo</th><th>IntraDose</th><th></th></tr><tr><td></td><td>(n= 62)</td><td>(n= 24)</td><td>(n=57)</td><td>(n=</td></tr><tr><td>35)</td><td></td><td></td><td></td><td></td></tr><tr><td>No. (%) of responses</td><td></td><td></td><td></td><td></td></tr><tr><td>Complete response (CR)</td><td>14 (23%)</td><td>0 (0%)</td><td>9 (16%)</td><td></td></tr><tr><td>1 (3%)</td><td></td><td></td><td></td><td></td></tr><tr><td>Partial response (PR)</td><td>7 (11%)</td><td>0 (0%)</td><td>5 (9%)</td><td></td></tr><tr><td>0 (0%)</td><td></td><td></td><td></td><td></td></tr><tr><td>Overall response</td><td>21 (34%)</td><td>0 (0%)</td><td>14 (25%)</td><td>1</td></tr><tr><td>(3%)</td><td></td><td></td><td></td><td></td></tr><tr><td>(CR + PR)</td><td></td><td></td><td></td><td></td></tr><tr><td>95% Confidence Interval</td><td>(22-47%)</td><td>(0-14%)</td><td>(14-38%)</td><td></td></tr><tr><td>(0.072-15%)</td><td></td><td></td><td></td><td></td></tr><tr><td>p value</td><td>0.001</td><td></td><td>0.007</td><td></td></tr></table> <p>Complete response (100% decrease in tumor volume sustained for at least 28 days)</p> <p>Partial response (<math>\geq 50\%</math> &lt; 100% decrease in tumor volume sustained for at least 28 days)</p>	Placebo	North America		Europe		IntraDose	Placebo	IntraDose			(n= 62)	(n= 24)	(n=57)	(n=	35)					No. (%) of responses					Complete response (CR)	14 (23%)	0 (0%)	9 (16%)		1 (3%)					Partial response (PR)	7 (11%)	0 (0%)	5 (9%)		0 (0%)					Overall response	21 (34%)	0 (0%)	14 (25%)	1	(3%)					(CR + PR)					95% Confidence Interval	(22-47%)	(0-14%)	(14-38%)		(0.072-15%)					p value	0.001		0.007		<p>Study 414-94-2 Vol. 4.15/pg. 1</p> <p>Study 514-94-2 Vol. 4.42/pg. 1</p>
Placebo		North America		Europe																																																																							
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<p><b><i>The overall response rate (CR + PR) for target tumors in the two studies combined was 29% (95% CI:21-38%); the overall complete response rate was 19%. In patients who responded, the median</i></b></p>	<p>ISE Section 3.1.3.4.1.1 Vol. 4.13/pg. 156</p>																																																																										

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<i>duration of response for the combined studies was 78 days (range 30 to 554+ days) and the median time to response was 21 days, after a median of two IntraDose treatments.</i>	
<i>The North American and European controlled studies included treatment of other tumors in addition to the target tumor. When all treated tumors in the two studies were assessed for response, the overall response rate (CR + PR) was 30% (68/227 treated tumors). For tumors that responded, the median response duration for individual treated tumors was 75 days.</i>	ISE Section 3.1.3.5.1 Vol. 4.13/pg. 180
<i>Patients who had received prior cisplatin or carboplatin therapy were as responsive to IntraDose treatment as those who had not been previously treated (29% and 30%, respectively).</i>	ISE Section 3.1.3.4.1.2 Vol. 4.13/pg. 160
<b>Clinical Benefit</b> <i>Clinical benefit was assessed in terms of its impact on quality of life (QoL) as measured by the attainment of primary treatment goals that were related to the target tumor and chosen prospectively by the patient and physician. Patients could choose a palliative goal such as pain control, wound care, obstructive symptoms, physical appearance, ability to see, hear or smell, or mobility. Physicians could select one of the palliative goals or a preventive goal such as prevention of invasion or obstruction of a vital structure or blood vessel or break through to the skin of subcutaneous tumors. For the two controlled studies combined, 27% of IntraDose treated patients achieved a clinical benefit compared to 12% of placebo patients (p=0.046).</i>	ISE Section 3.1.2.2 Vol. 4.13/pg. 135  ISE Section 3.1.3.4.2.1 Vol. 4.13/pg. 167
<b>Tumor response and clinical benefit were significantly associated</b>	ISE Section

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<p><b><i>(p=0.006). Patients who had a response of the target tumor were nearly 2.5 times more likely to attain a clinical benefit from treatment than patients who did not have a response of the target tumor (46% versus 19%, respectively).</i></b></p>	<p>3.1.3.4.3 Vol. 4.13/pg. 178</p>
<p><b>Other Solid Tumors</b></p> <p>Two open-label studies were conducted in 126 patients with solid tumors that were metastatic or recurrent from various primary sites. Cancers included breast cancer, melanoma and esophageal cancer as well as a wide variety of other symptomatic cancers. Most of these patients (91%) had received previous treatment and the majority (73%) had received multiple prior therapies. Patients received weekly injections of 0.5 mL of IntraDose per cm<sup>3</sup> of tumor for up to 6 weeks. Objective tumor response and clinical benefit were evaluated for the target tumor as described above for the placebo-controlled head and neck cancer studies. In patients with breast adenocarcinoma (n = 28), the response of the target tumor was 50% with a median duration of 82 days (29-211 days). Clinical benefit was attained in 39% of patients and there was a significant association with tumor response (p = 0.033). For patients with malignant melanoma (n = 27), the response rate was 33% with a median duration of 72.5 days (30-632 days). For esophageal cancer patients (n = 24), the response rate was 29% with a median duration of 84 days (29-120 days).</p>	<p>ISE Section 3.2.3.2.1 Vol. 4.13/pg. 191 ISE Section 3.2.3.2.2 Vol. 4.13/pg. 193 ISE Section 3.2.2 Vol. 4.13/pg. 189</p> <p>ISE Section 3.2.3.4.1 Vol. 4.13/pg. 197</p> <p>ISE Section 3.2.3.5 Vol. 4.13/pg. 200 ISE Section 3.2.3.4.1 Vol. 4.13/pg. 197</p>
<p>The overall objective response rate (CR and PR) for the primary target tumor in the combined studies was 35%. The overall clinical benefit rate was 31%. Of those patients who had a response, 52% attained a clinical benefit. The association between clinical benefit and response of the target tumor was statistically significant (p=0.0001).</p>	<p>ISE Section 3.2.3.4.1 Vol. 4.13/pg. 197 ISE Section 3.2.3.4.2 Vol. 4.13/pg. 199 ISE Section 3.2.3.5 Vol. 4.13/pg. 200</p>

Labeling Text	NDA Cross Reference Volume/Page
<p><b>INDICATIONS AND USAGE</b></p> <p>IntraDose® (cisplatin/epinephrine) Injectable Gel is indicated for the treatment of recurrent or refractory squamous cell carcinoma of the head and neck in patients who are not considered curable with surgery or radiotherapy. The safety and efficacy of IntraDose in the treatment of individual tumors &gt;20 cm<sup>3</sup> has not been established.</p>	
<p><b>CONTRAINDICATIONS</b></p> <p>IntraDose should not be used for the treatment of any tumor that directly involves or threatens to invade the carotid or vertebral artery. In these patients, the potential risk of cerebral vascular complications, including cerebral vascular accidents, outweighs the potential benefit from tumor regression.</p> <p>Patients with known hypersensitivity to any of the components in IntraDose, including cisplatin, bovine collagen, epinephrine or sulfites, should not be treated.</p>	<p>ISS Section 18 Vol. 4.13/pg. 307</p>

Labeling Text	NDA Cross Reference Volume/Page
<p><b>WARNINGS</b></p> <p><b>Caution:</b> IntraDose should only be administered by direct intratumoral injection. IntraDose <b>MUST NOT</b> be injected intravenously, intra-arterially, or intrathecally. Injection into or adjacent to a major blood vessel may cause bleeding, arterial vasospasm or vascular occlusion. In situations where there are complex anatomical relationships, use of imaging procedures to guide the injection of the drug may be advisable. Injection of IntraDose may involve a risk of damage to adjacent peripheral or cranial nerves (see PRECAUTIONS).</p>	<p>ISS Section 18 Vol. 4.13/pg. 307</p> <p>ISS Section 19.10 Vol. 4.13/pg. 314</p>
<p><b>Local Reactions:</b> Injection of IntraDose into tumors results in a high intratumoral concentration of cisplatin for an extended period of time. Expected local cytotoxic effects in the tumor and adjacent tissue may include erythema, swelling, erosion, ulceration, necrosis, eschar formation and/or bleeding. The incidence of local cytotoxic effects generally peaks 2 weeks after the start of treatment and resolves over the next 3-12 weeks. In clinical studies, many patients had these tissue conditions at baseline, although most of these were mild to moderate in severity. Following treatment with IntraDose, the overall incidence and severity of local cytotoxic reactions increased in the IntraDose group. However, most of these effects were mild to moderate and resolved with standard wound care measures.</p>	<p>ISS Section 7 Vol. 4.13/pg. 285 ISS Section 19.12 Vol. 4.13/pg. 314</p>
<p>Patients at risk for delayed wound healing due to prior surgery, radiation, poor nutrition or inadequate blood supply may be at higher risk for developing more severe local cytotoxic effects. In cases where administration of the next scheduled IntraDose treatment might be expected to intensify the severity of existing local cytotoxic effects, especially ulceration and necrosis, treatment with IntraDose should be delayed until there is adequate healing of the tumor or surrounding tissue (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).</p>	<p>ISS Section 19.12 Vol. 4.13/pg. 314</p>
<p><b>Allergic Reactions:</b> Anaphylactic-like reactions to platinum-containing</p>	<p>Platinol Package</p>

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<p>products have been reported to occur within minutes of systemic administration in patients with prior exposure to similar compounds. The safety of IntraDose in patients with a history of anaphylaxis or a history of multiple severe allergies has not been demonstrated. Patients with a history of dietary beef allergy should be carefully evaluated before injection with products containing bovine collagen because such patients may be predisposed to allergic reaction to any bovine-derived product.</p>	<p>Insert Vol. 4.160/pg. 135</p> <p>ISS Section 18 Vol. 4.13/pg. 307</p>
<p>IntraDose contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and severe or even life-threatening asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and is probably low. Sulfite sensitivity is more frequent in asthmatic than in nonasthmatic people.</p>	<p>21 CFR 201.22 (b)</p>
<p><b>Pregnancy:</b> IntraDose should not be used in patients who are pregnant, lactating or breast feeding. Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin has been shown to be mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. Patients should be advised to avoid becoming pregnant during IntraDose therapy. If IntraDose is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.</p>	<p>Platinol Package Insert Vol. 4.160/pg. 135</p>
<p><b>PRECAUTIONS</b> <b>General: Not for intravenous injection.</b> IntraDose should only be administered by direct intratumoral injection and <b>MUST NOT</b> be injected intravenously, intra-arterially or intrathecally (see WARNINGS).</p> <p>Physicians administering this product should be familiar with the local and</p>	<p>ISS Section 18 Vol. 4.13/pg. 307</p>

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<p>surgical anatomy of the site of injection. Imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) may be required prior to treatment with IntraDose in order to adequately define the local anatomy and to plan the approach and extent of the local injection. In some patients, imaging guidance with ultrasound or CT may assist needle placement at the site of injection.</p>	
<p>Local injection of IntraDose involves a risk of serious adverse experiences such as hemorrhage or cerebral vascular events, especially with tumors involving major vessels of the extracranial vascular system. Tissue damage, needle trauma to the artery, chemical irritation, mechanical pressure from a large injected volume, local inflammation and swelling or tumor progression alone or in combination with IntraDose may contribute to the occurrence of cerebral vascular events.</p>	<p>ISS Section 18 Vol. 4.13/pg. 307</p>
<p><b>Pain Management: A comprehensive pain management program should be planned for each patient prior to treatment. The physician should assess the patient's pain prior to injection and anticipate the possibility that pain will be increased during and following the injection of IntraDose. Sufficient time should be allowed for any anesthetic or analgesia to take effect prior to administration of IntraDose. It may be valuable to obtain consultation from an anesthesiologist or other pain-management specialist. Topical and other local anesthetics, loco-regional nerve blocks and systemic analgesics may be used alone or in combination, as appropriate. If a local anesthetic is used, it should be injected around the tumor margins.</b> Local anesthetics containing epinephrine are contraindicated.</p> <p>It should be assumed that narcotic-strength analgesia will be required at least for the first IntraDose administration procedure. Narcotic-strength analgesia with parenteral morphine sulfate, meperidine or fentanyl has been used in clinical trials of IntraDose, frequently in combination with lorazepam. An alternative regimen may involve local anesthesia with lidocaine and administration of midazolam hydrochloride. Provisions should be made to continue adequate analgesia for 24-48 hours following the procedure,</p>	<p>ISS Section 5.3.1 Vol. 4.13/pg. 267</p>

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<p>during which time treatment with narcotic strength analgesics may be required. Subsequently, nonsteroidal anti-inflammatory drugs or acetaminophen may be adequate for pain management.</p>	
<p><b>Wound Care:</b> Local infection may occur, particularly in previously irradiated areas or in areas with pre-existing ulceration and necrosis, where facultative anaerobes and other pathogens may thrive. Cellulitis was reported infrequently in clinical studies. Management of local infection during IntraDose therapy, with local wound care or systemic antibiotics, may be necessary. The local cytotoxic effects of IntraDose on treated tumors may include erythema, swelling, erosion, ulceration, necrosis, eschar and/or bleeding (see WARNINGS). Patients at risk for delayed wound healing due to prior surgery, radiation, poor nutrition or inadequate blood supply may be at higher risk for developing more severe local cytotoxic effects.</p>	<p>ISS Section 19.4 Vol. 4.13/pg. 312</p> <p>ISS Section 7 Vol. 4.13/pg. 285</p>
<p><b>Renal Effects and Dehydration:</b> The low systemic exposure to cisplatin released from IntraDose is not expected to produce direct renal toxicity. Nevertheless, patients with advanced head and neck cancer frequently have poor oral intake and may be both dehydrated and poorly nourished. This may be especially true for elderly patients, who are also more likely to have decreased renal function. Oral intake may be further compromised in the days following IntraDose treatment due to the local cytotoxic effects of the drug or from anorexia associated with concurrent narcotic analgesics. In these patients, the need for adequate hydration and/or intravenous fluid replacement should be considered.</p>	<p><b>Final report 43-93-P- PK</b> <b>Vol. 4.12/pg. 50</b></p> <p>ISS Section 6.1.3 Vol. 4.13/pg. 272</p> <p>ISS Section 6.1.5 Vol. 4.13/pg. 277</p>
<p><b>Information for Patients:</b> Patients should be informed of the expected effects of IntraDose, in particular, the likelihood of increased pain during and after injection. Patients should also be made aware that treatment may result in local skin reactions, such as erythema, swelling, erosion,</p>	<p>ISS Section 6.1.1 Vol. 4.13/pg. 270</p> <p>ISS Section 6.1.2 Vol. 4.13/pg. 271</p>

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<p>ulceration, necrosis, eschar formation and/or bleeding or a worsening of these conditions that may be present before treatment with IntraDose. These effects occur within days of treatment and may become worse as treatments proceed before improvement is noted.</p>	<p>ISS Section 7.2 Vol. 4.13/pg. 286</p>
<p><b>Drug Interactions:</b> No formal drug interaction studies have been conducted. In addition, the short and long-term toxicity profiles of IntraDose, when given concurrently with radiation or systemic chemotherapy, have not been studied.</p>	<p>ISS Section 15 Vol. 4.13/pg. 307</p>
<p><b>Carcinogenesis, Mutagenesis, Impairment of Fertility:</b> The carcinogenic potential of IntraDose has not been studied. Cisplatin has been shown to be mutagenic in bacteria and produce chromosome aberrations in animal cells in tissue culture. In mice cisplatin is teratogenic and embryotoxic (see WARNINGS).</p>	<p>Platinol Package Insert Vol. 4.160;pg. 135</p>
<p><b>Pregnancy:</b> Category D. Safe use during human pregnancy has not been established (see WARNINGS) .</p>	<p>Platinol Package Insert Vol. 4.160;pg. 135</p>
<p><b>Nursing Mothers:</b> The safety of IntraDose use in nursing mothers has not been established. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IntraDose, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.</p>	<p>21 CFR.57(f)(8)</p>
<p><b>Pediatric Use:</b> The safety and effectiveness of IntraDose in pediatric patients has not been established.</p>	<p>21 CFR 201.57(f)(9)</p>

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<p><b>Geriatric Use:</b> Of the total number of subjects in clinical studies of IntraDose, 37% percent were 65 and over, while 15% percent were 75 and over. No overall differences in safety or effectiveness were observed between these and younger subjects.</p>	<p>21 CFR 201.57(f)(10)</p>
<p><b>ADVERSE REACTIONS</b> The total safety database is comprised of 396 patients treated in five IntraDose clinical studies. Of these, 225 patients (150 IntraDose/75 placebo) were treated in the North American and European controlled studies; 171 patients were treated in open-label studies. Approximately 120 of these patients received 6 or more IntraDose treatments.</p>	<p>ISS Section 1.3 Vol. 4.13/pg. 245</p>
<p>The most frequent treatment-related adverse events in the North American and European placebo-controlled studies were either immediate injection effects (pain, tachycardia or hypertension) or local reactions at the treatment site (pain, facial edema, hemorrhage, infection, neck pain or pruritis). Overall, pain was the most frequent adverse event. Some patients randomized to IntraDose or placebo experienced transient elevation of blood pressure and pulse rate during the administration of the treatment. In a few cases, these were judged to be clinically significant hypertension or tachycardia, possibly due to the injected epinephrine or the result of anxiety that accompanied injection.</p>	<p><b>ISS Table S-20</b> <b>Vol. 4.128/pg. 1</b></p> <p><b>ISS Section 11.2</b> <b>Vol. 4.13/pg. 304</b> <b>ISS Section 18</b> <b>Vol. 4.13/pg. 307</b></p>
<p>The most clinically important adverse reactions observed in clinical studies with IntraDose were cerebrovascular events, cardiovascular events and significant tissue damage caused by the local cytotoxic effects of IntraDose.</p>	<p>ISS Section 18 Vol. 4.13/pg. 307 ISS Table S- 20 Vol. 4.128/pg. 1</p>
<p>The low systemic absorption of cisplatin after intratumoral injection of IntraDose formulation is evident in the small number of adverse events that are typically attributed to systemically administered cisplatin. The most frequently reported systemic events were nausea and vomiting, asthenia and headache. These adverse events were generally mild to moderate in severity and effectively managed with supportive measures. Treatment</p>	<p>ISS Section 19 Vol. 4.13/pg. 310</p>

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discontinuation or delay was usually not necessary.																																														
<p><u>Adverse Events Occurring in ≥5% of</u> <b>Patients in the Placebo-Controlled Studies</b> <b>(Treatment Related*)</b></p> <table><thead><tr><th></th><th><u>IntraDose</u> n = 150</th><th><u>Placebo</u> <u>(collagen gel only)</u> n = 75</th></tr></thead><tbody><tr><td>Pain</td><td>40% (60)</td><td>25% (19)</td></tr><tr><td>    Within 15 min. of injection</td><td>25% (37)</td><td>19% (14)</td></tr><tr><td>    Localized at treatment site</td><td>25% (37)</td><td>12% (9)</td></tr><tr><td>Face Edema</td><td>11% (17)</td><td>1% (1)</td></tr><tr><td>Hemorrhage</td><td>9% (13)</td><td>5% (4)</td></tr><tr><td>Infection</td><td>9% (13)</td><td>3% (2)</td></tr><tr><td>Nausea</td><td>8% (12)</td><td>3% (2)</td></tr><tr><td>Hypertension</td><td>8% (12)</td><td>5% (4)</td></tr><tr><td>Neck Pain</td><td>8% (12)</td><td>1% (1)</td></tr><tr><td>Vomiting</td><td>7% (10)</td><td>1% (1)</td></tr><tr><td>Headache</td><td>7% (10)</td><td>1% (1)</td></tr><tr><td>Pruritus</td><td>6% (9)</td><td>3% (2)</td></tr><tr><td>Tachycardia</td><td>6% (9)</td><td>3% (2)</td></tr><tr><td>Asthenia</td><td>5% (7)</td><td>1% (1)</td></tr></tbody></table> <p>*Patients may have experienced adverse events in more than one category and may be counted more than once.</p>		<u>IntraDose</u> n = 150	<u>Placebo</u> <u>(collagen gel only)</u> n = 75	Pain	40% (60)	25% (19)	Within 15 min. of injection	25% (37)	19% (14)	Localized at treatment site	25% (37)	12% (9)	Face Edema	11% (17)	1% (1)	Hemorrhage	9% (13)	5% (4)	Infection	9% (13)	3% (2)	Nausea	8% (12)	3% (2)	Hypertension	8% (12)	5% (4)	Neck Pain	8% (12)	1% (1)	Vomiting	7% (10)	1% (1)	Headache	7% (10)	1% (1)	Pruritus	6% (9)	3% (2)	Tachycardia	6% (9)	3% (2)	Asthenia	5% (7)	1% (1)	ISS Section 20 Vol. 4.13/pg. 316
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<p>Selected treatment-related adverse reactions that occurred in 2-4% of patients in the two placebo-controlled studies are presented below in descending order of frequency. Included are clinically significant adverse reactions that occurred in 1% or less of patients regardless of relationship to treatment.</p> <p><b>Body as a whole:</b> Fever, cellulitis, chest pain, fistula, allergic reaction</p> <p><b>Cardiovascular:</b> Vasodilatation, palpitation, hypotension, vasospasm, cerebrovascular accident, arteriospasm, cerebral ischemia, cerebral infarct, heart arrest</p> <p><b>Digestive:</b> Anorexia, dysphagia, diarrhea, tongue edema</p> <p><b>Hemic and Lymphatic:</b> Anemia, leukocytosis</p> <p><b>Metabolic and Nutritional:</b> Edema, weight loss, hypomagnesemia,</p>	ISS Table S-18 Vol. 4.127/pg. 58 ISS Table S-20 Vol. 4.128/pg. 1																																													

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<p>dehydration, hypercalcemia</p> <p><b>Musculoskeletal:</b> Joint disorder</p> <p><b>Nervous:</b> Dizziness, paresthesia, tremor, neuropathy, paralysis, facial paralysis, convulsion, hemiplegia</p> <p><b>Respiratory:</b> Dyspnea</p> <p><b>Skin and appendages:</b> Drainage, drainage serosanguinal, sweating</p> <p><b>Special senses:</b> Tinnitus, blindness, deafness</p>	
<p>Clinically important adverse events observed in patients treated in five IntraDose clinical studies (n=396) are described below:</p>	
<p><b>Cerebrovascular Events:</b> During the early portion of the North American placebo-controlled study, a total of six patients experienced a cerebrovascular event (5 IntraDose, 1 placebo). All of the events occurred during or shortly (within 1 to 2 hr) after treatment. These events were judged to be treatment related and most likely caused by carotid artery vasospasm. No events occurred after patients with tumors invading or threatening to invade the carotid artery were excluded from the study. The respective etiologies of these events have not been defined with certainty, and head and neck cancer itself, a known predisposing factor in cerebrovascular events, is listed among other possible causes that cannot be ruled out. Extreme care must be exercised when injecting IntraDose, particularly in areas where there are complex anatomical relationships (see CONTRAINDICATIONS and PRECAUTIONS).</p>	<p>ISS Section 18 Vol. 4.13/ pg. 307</p>
<p><b>Cardiovascular Events:</b> Cardiovascular-related events, including tachycardia (15), hypertension (23), palpitations (4) were reported in 58 (15%) IntraDose or placebo treated patients in five clinical studies. Of these events, only 12 (3%) were considered severe. One patient experienced a non-fatal cardiopulmonary arrest following injection with IntraDose. The etiology of</p>	<p>ISS Table S-20 Vol. 4.128/pg. 1</p> <p>ISS Section 9.1 Vol. 4.13/pg. 297</p>

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<p>this event has not been determined; however, the patient had a history of hypertension and peripheral vascular arteriosclerotic disease and a prior cardiac arrest of unknown etiology.</p>	
<p><b>Significant Tissue Damage:</b> Local cytotoxic effects may result in erosion, ulceration, bleeding or fistula formation. Spontaneous hemorrhage occurred in 22 (6%) of patients. Most of these events were mild or moderate in severity. In 3 cases, the hemorrhage was severe and led to death of the patient. The possible etiologies of these events include necrosis of a tumor that involves a blood vessel (e.g. carotid artery) and tumor necrosis secondary to local cytotoxic effects of cisplatin. Caution is advised in treating tumors that are friable or bleeding. Breakdown of tumor tissue and disease progression affecting adjacent tissue can lead to superficial bleeding and fistula development. Fistulae were reported in 10 (3%) patients (9 IntraDose, 1 placebo).</p>	<p>ISS Table S-20 Vol. 4.128/pg. 1 ISS Section 10 Vol. 4.13/pg. 302</p>
<p><b>Allergic Reactions:</b> Four patients treated with IntraDose had an allergic reaction. One patient had an anaphylactoid reaction following IntraDose treatment. A second patient had an anaphylactoid reaction to systemically administered cisplatin after completing local treatment with IntraDose and may have developed sensitivity to cisplatin following local treatment. Two other patients had immediate local allergic-like reactions limited to the site of injection. Because the causes of these allergic reactions are not known, the risk of allergic reaction to any component of IntraDose must be considered (See CONTRAINDICATIONS and WARNINGS).</p>	<p>ISS Table S-18 Vol. 4.127/pg. 58</p>
<p><b>OVERDOSAGE</b></p> <p>Caution should be exercised to prevent inadvertent overdosage with IntraDose. An overdosage may cause excess local cytotoxic effects and can lead to development of an ulcer or fistula. There is no known antidote</p>	<p>Drug Abuse and Overdosage Vol. 4.13/pg. 343</p>

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<p>for IntraDose overdosage. Management of overdosage should include general supportive care to sustain the patient through any period of toxicity that may occur. Supportive care may involve intravenous hydration and routine wound care measures for the management of any local cytotoxic effects in surrounding normal tissues.</p>	
<p>A 10-mL dose of IntraDose contains 1 mg epinephrine. Patients with cardiovascular disease may be at increased risk of adverse events attributable to epinephrine. Patients with pre-existing hypertension should have their blood pressure adequately controlled. Epinephrine overdosage may result in extremely elevated arterial pressure, increased risk of cerebrovascular accident, pulmonary edema, transient bradycardia followed by tachycardia, and potentially fatal cardiac arrhythmias, or ventricular premature contractions. Other reported effects may include extreme pallor and coldness of the skin, metabolic acidosis and kidney failure. Patients treated for epinephrine overdose should receive appropriate supportive care.</p>	<p>ISS Section 18 Vol. 4.13/pg. 307</p>
<p><b>DOSAGE AND ADMINISTRATION</b></p> <p>Physicians administering this product should be familiar with the local and surgical anatomy of the site of injection. In addition, to reduce the possibility of cardiovascular complications, patient blood pressure and pulse should be monitored regularly during treatment.</p> <p>Radiological imaging studies with CT, MRI, ultrasound or other specialized radiological techniques may be required to accurately identify the extent of local tumor involvement and to plan the treatment program for local tumor injection (see PRECAUTIONS).</p> <p>Treat each tumor with 0.25 mL IntraDose per cm<sup>3</sup> of tumor volume to a</p>	<p>ISS Section 18 Vol. 4.13/pg. 307</p> <p>ISE 3.1.2.1 Vol. 4.13/pg. 130</p>

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<p>maximum of 10 mL of IntraDose administered at any one visit. One or more tumors may be treated on any one treatment day. IntraDose should be administered on a weekly basis for up to 6 treatments (one cycle). Estimate tumor volume by physical examination or imaging studies using the three tumor dimensions (length x width x height x 0.5). At each treatment visit, the tumor volume should be remeasured and the dose volume recalculated, as needed. Additional treatment cycles can be administered if the tumor progresses or as new tumors develop.</p> <p>Tumors treated with IntraDose should be monitored on a weekly basis to assess the effect of treatment on tumor regression, as well as any local cytotoxic effects on the tumor and adjacent tissues (see WARNINGS). If needed, treatment should be delayed for one week or until there is adequate healing of any local cytotoxic effects in the tumor or surrounding tissue.</p>	
<p>Preparation Instructions: <b>Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.</b></p> <p>Aseptic techniques should be employed during preparation of IntraDose. Precautions appropriate for the handling of antineoplastic agents should be exercised including preparation under a laminar flow hood (see DOSAGE AND ADMINISTRATION; Storage and Handling).</p> <p>Needles containing aluminum parts that may come in contact with IntraDose should not be used for preparation or administration. Aluminum reacts with cisplatin, causing precipitate formation and a loss of potency.</p>	<p>Platinol Package Insert Vol. 4.160/pg. 135</p>
<p>No components of the kits should be substituted. <b>Components of IntraDose must not be substituted with other forms of lyophilized cisplatin, epinephrine solution or collagen gel, as the IntraDose components are each uniquely formulated for use in IntraDose. The use of other formulations of these components will</b></p>	<p>Vol. 2.1/pg. 47</p>

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<p><b>result in a physically or chemically different product that could affect the efficacy or safety of the preparation.</b></p> <p>Remove kit from refrigerator and allow to warm to room temperature for at least 5 minutes.</p> <p>Attach the sterile 22-gauge needle provided in the kit to the empty sterile 3-cc syringe. Withdraw 1.7 mL of IntraEpi (epinephrine solution), and transfer into the vial of IntraPlatin (cisplatin for injectable suspension). Discard the IntraEpi vial and remaining contents.</p>	
<p>Swirl the IntraPlatin vial for 30 seconds to yield a homogeneous suspension. Invert the vial and, while gently swirling, withdraw 1.5 mL of the reconstituted IntraPlatin suspension into the 3-cc syringe. Remove and discard the needle upon completion of withdrawal.</p> <p>Remove the IntraGel syringe from the kit, remove its rubber tip cap and attach the Luer-lock syringe connector.</p> <p>Attach the syringe containing the IntraPlatin suspension on the syringe connector attached to the IntraGel syringe. Make sure the connections are secure and then slowly transfer the suspension into the IntraGel syringe. Pushing the plunger gently will eject the outer stopper from the IntraGel syringe. Affix the plunger rod into the IntraGel syringe by placing the threaded end into the syringe barrel and screwing it gently into the inner (remaining) rubber plunger. With both syringes securely fastened to the syringe connector, rapidly transfer the contents back and forth between syringes for 30 seconds (30 strokes forward and 30 strokes backward) to effect complete mixing.</p>	Vol. 2.1/pg. 47
<p>Complete the mixing with all the contents in the 3-cc (plastic) syringe. Remove and discard the empty glass syringe and Luer-lock syringe connector; then attach a suitable sterile administration needle to the 3-cc</p>	

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<p>syringe containing the final mixed IntraDose Injectable Gel. The needle for patient injection is not included in the IntraDose kit.</p> <p>Preparation as specified results in 2 mL of a viscous, opaque, pale yellow gel containing 8.0 mg of cisplatin and 0.2 mg of epinephrine.</p> <p>NOTE: Discard 4 hours after mixing.</p>	<p>Vol. 2.1/pg. 59</p> <p>Vol. 2.1/pg. 78</p>
<p><b>Intratumoral Injection Technique:</b> The precise anatomical localization of the tumor should be well defined by physical examination or pretreatment CT, MRI or x-ray studies. If the exact placement of injections cannot be performed by visual guidance and physical examination, imaging guidance and monitoring of the procedure with ultrasound or CT scan may be necessary. Imaging-guidance is recommended for injection of tumors that may be impinging on major arteries, especially when the local anatomy has been altered by surgery or radiation. Care should be taken in order to avoid unintentional injection of IntraDose into a blood vessel (See PRECAUTIONS).</p>	<p>ISS Section 18 Vol. 4.13/pg. 307</p>
<p>Using a small (22 to 25 gauge) needle attached to a Luer-lock syringe, insert the needle into the base of the tumor at approximately a 45-degree angle. Pull back gently on the plunger. If blood appears, withdraw the needle and repeat. If blood does not appear, proceed with administration. Depending on the size and location of the tumor, the injection may be done by tracking the product through the tumor from a single puncture site or by injecting the tumor from multiple sites in parallel rows approximately 0.5 to 1.0 cm apart.</p>	

# Attachment 1

## Cisplatin/Epinephrine Gel Formulations

Ingredient	Content (in mg/mL unless otherwise indicated)		
	CDDP/epi gel (prototype)	CDDP gel	CDDP/epi gel (revised)**
cisplatin	4.0	4.0	4.0
epinephrine	0.1	—	0.1
collagen	20	20	20
sodium phosphates	30 mM	30 mM	30 mM*
mannitol	40	40	40
sodium chloride	38	37	37
chlorobutanol	0.5	—	—
edetate disodium dihyd	—	—	0.05
sodium bisulfite	≤ 0.15	—	—
sodium metabisulfite	—	—	0.13
polysorbate 80	—	—	0.66
glacial acetic acid	—	—	0.32
sodium acetate	—	—	0.10
Water for Injection	qs	qs	qs
HCl and/or NaOH	pH adjust	pH adjust	pH adjust

\* the sodium phosphates concentration is now expressed in terms of the two individual sodium phosphate salts ( $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$  and  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ ) in mg/mL (1.4 and 5.4, respectively)

\*\* proposed commercial formulation

Summaries of the completed studies are provided below. A full report of the pharmacokinetics portion of Study 43 and a draft manuscript of the Johnson study prepared for publication are also provided in the Human Pharmacokinetics and Bioavailability section of this submission.

Table 14.2-02 Clinical Profile of Patients

Patient No.	Age (yr)	Sex	Body Wt (kg)	Surface Area (m <sup>2</sup> )	Dosing Date(s)	Treated Tumor Location(s)	Treated Tumor Vol (cm <sup>3</sup> )	Gel Dose (mL)	Dosing Duration (min)	Admin Dose of CDDP (mg)	Admin Dose of CDDP (mg/kg)	Admin Dose of CDDP (mg/m <sup>2</sup> )
8335	60	M	86.0	2.02	09 May 00 (Dose 1)	face	20.0	4.0	2	16.0	0.186	7.92
8342	55	F	42.5	1.34	28 Jun 00 (Dose 3)	neck (2)	22.0	5.5	20	22.0	0.518	16.4
8345	67	M	51.0	1.53	26 Jul 00 (Dose 1)	neck	10.5	2.625	3	10.5	0.206	6.86
			51.0	1.53	16 Aug 00 (Dose 3)	neck	10.5	2.625	3	10.5	0.206	6.86
8346	51	M	55.0	1.58	30 Aug 00 (Dose 1)	neck	15.0	3.75	2	15.0	0.273	9.49
			55.0	1.58	13 Sep 00 (Dose 3)	neck	15.0	3.75	2	15.0	0.273	9.49
8347	53	F	58.0	1.61	30 Aug 00 (Dose 1)	neck	12.0	3.0	2	12.0	0.207	7.45
8348	40	M	60.0	1.71	05 Sep 00 (Dose 1)	neck, face (2)	18.6	4.6	10	18.4	0.307	10.8
8349	48	M	49.0	1.51	25 Sep 00 (Dose 1)	mouth	20.0	4.5	12	18.0	0.367	11.9
8350	65	M	60.5	1.69	10 Oct 00 (Dose 1)	mouth, neck	25.5	6.4	19	25.6	0.416	14.9
8351	48	M	47.5	1.48	25 Oct 00 (Dose 1)	neck	15.6	4.0	3	16.0	0.337	10.8
8352	64	M	80.0	1.96	8 Nov 00 (Dose 1)	neck	18.8	4.7	3	18.8	0.235	9.59
			80.0	1.96	22 Nov 00 (Dose 3)	neck	18.8	4.7	3	18.8	0.235	9.59
8354	54	M	60.5	1.68	1 Dec 00 (Dose 1)	neck	15.0	3.8	10	15.2	0.251	9.05
8415	43	M	76.0	1.93	27 Dec 00 (Dose 3)	neck	16.0	4.0	3	16.0	0.211	8.29
8416	51	F	37.0	1.25	3 Jan 01 (Dose 1)	neck	16.9	4.6	12	16.0	0.432	12.8
8417	58	M	63.0	1.69	21 Dec 00 (Dose 1)	neck	13.5	3.4	3	13.6	0.216	8.05
			63.0	1.69	4 Jan 01 (Dose 3)	neck	13.5	3.4	3	13.6	0.216	8.05
8418	64	M	46.0	1.46	9 Jan 01 (Dose 1)	mouth	18.4	4.6	10	18.4	0.400	12.6
8419	59	M	58.0	1.64	8 Jan 01 (Dose 1)	mouth	16.9	4.2	8	16.8	0.290	10.2

Table 14.2-06 Summary of Pharmacokinetic Parameters for Total Platinum

	Patient No.											
	8335	8342	8345	8346	8347	8348	8349	8350	8351			
	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 1	Dose 1	Dose 1	Dose 1	Dose 1
Dose CDDP (mg)	16.0	22.0	10.5	10.5	15.0	15.0	12.0	18.4	18.0	25.6	16.0	
Dose Pt (mg)	10.4	14.3	6.8	6.8	9.8	9.8	7.8	12.0	11.7	16.6	10.4	
Body Weight (kg)	86.0	42.5	51.0	51.0	55.0	55.0	58.0	60.0	49.0	61.5	47.5	
Surface Area (m <sup>2</sup> )	2.02	1.34	1.53	1.53	1.58	1.58	1.61	1.71	1.51	1.72	1.48	
C <sub>max</sub> (ng/mL)	251	256	147	147	352	231	161	267	259	384	132	
t <sub>max</sub> (h)	24	2	1	48	0.08	24	4.5	4.5	24	2	24	
AUC <sub>0-1</sub> (μg·h/mL)	30.1	32.5	20.7	6.17	22.2	33.3	6.88	7.9	10.9	37.2	5.95	
AUC <sub>0-∞</sub> (μg·h/mL)	56.1	47.2	46.0	50.6	67.6	127.2	89.2	17.1	53.7	60.7	—	
MRT <sub>0-1</sub> (h)	83	89	97	25	89	91	24	20	24	94	25	
MRT <sub>0-∞</sub> (h)	243	186	362	373	477	615	581	80	213	236	—	
Cl (L/h)	0.185	0.371	0.148	0.135	0.144	0.077	0.087	0.703	0.217	0.274	—	
Cl (mL/h/kg)	2.15	8.62	2.91	2.65	2.62	1.40	1.50	11.72	4.43	4.53	—	
V <sub>z</sub> (L)	47.4	57.7	53.6	49.3	6.8	46.7	50.6	59.1	47.0	6.9	—	
V <sub>z</sub> (L/kg)	0.551	1.358	1.051	0.967	0.124	0.849	0.872	0.985	0.959	0.112	—	
Terminal t <sub>1/2</sub> (h)	164	132	250	253	323	420	401	58	150	176	—	

— Cannot be estimated.

Table 14.2-06, continued Summary of Pharmacokinetic Parameters for Total Platinum

	Patient No.										Mean $\pm$ SE
	8352	8354	8415	8416	8417	8418	8419				
	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	
Dose CDDP (mg)	18.8	18.8	15.2	16.0	16.0	16.0	13.6	13.6	18.4	16.8	16.4 $\pm$ 0.8
Dose Pt (mg)	12.2	12.2	9.75	10.4	10.6	10.6	8.9	8.9	12.0	11.0	10.7 $\pm$ 0.5
Body Weight (kg)	80	80	60.5	76	37	63	63	63	46	58	59.1 $\pm$ 2.9
Surface Area (m <sup>2</sup> )	1.96	1.96	1.68	1.93	1.25	1.69	1.69	1.69	1.46	1.64	1.64 $\pm$ 0.05
C <sub>max</sub> (ng/mL)	274	346	247	419	206	327	307	307	176	149	252 $\pm$ 19
t <sub>max</sub> (h)	2.00	1.00	0.67	2.00	0.33	4	24	24	1	2.00	9.8 $\pm$ 2.9
AUC <sub>0-<math>\infty</math></sub> ( $\mu$ g·h/mL)	12.4	11.6	7.5	10.5	7.4	9.0	14.1	14.1	6.5	3.8	14.8 $\pm$ 2.4
AUC <sub>0-<math>\infty</math></sub> ( $\mu$ g·h/mL)	251.2	77.1	234.1	46.5	11.3	14.7	252.3	252.3	125.4	26.2	87.1 $\pm$ 17.8
MRT <sub>0-<math>\infty</math></sub> (h)	947	23	25	22	24	19	24	24	25	22	90 $\pm$ 46
MRT <sub>0-<math>\infty</math></sub> (h)	948	293	1374	187	51	51	833	833	843	308	434 $\pm$ 81
Cl (L/h)	0.049	0.155	0.038	0.220	0.775	0.581	0.036	0.036	0.091	0.390	0.25 $\pm$ 0.05
Cl (mL/h/kg)	0.62	1.94	0.63	2.89	20.95	9.22	0.57	0.57	1.98	6.72	4.6 $\pm$ 1.2
V <sub>z</sub> (L)	46.1	45.1	52.3	41.2	26.2	28.3	30.0	30.0	76.5	118.9	46.9 $\pm$ 5.3
V <sub>z</sub> (L/kg)	0.576	0.564	0.864	0.542	0.710	0.449	0.476	0.476	1.663	2.050	0.83 $\pm$ 0.10
Terminal t <sub>1/2</sub> (h)	657	202	947	130	23	34	578	578	581	211	299 $\pm$ 56

Table 14.2-07 Summary of Pharmacokinetic Parameters for Free Platinum

	Patient No.											
	8335	8342	8345		8346		8347	8348	8349	8350	8351	
	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 1	Dose 1	Dose 1	Dose 1	
Dose CDDP (mg)	16.0	22.0	10.5	10.5	15.0	15.0	12.0	18.4	18.0	25.6	16.0	
Dose Pt (mg)	10.4	14.3	6.8	6.8	9.8	9.8	7.8	12.0	11.7	16.6	10.4	
Body Weight (kg)	86.0	42.5	51.0	51.0	55.0	55.0	58.0	60.0	49.0	61.5	47.5	
Surface Area (m <sup>2</sup> )	2.02	1.34	1.53	1.53	1.58	1.58	1.61	1.71	1.51	1.72	1.48	
C <sub>max</sub> (ng/mL)	47	44	90	27	177	15	67	135	141	229	104	
t <sub>max</sub> (h)	0.67	1	0.67	2	0.08	0.08	0.67	0.67	0.67	1	0.08	
AUC <sub>0-11</sub> (μg·h/mL)	0.400	0.136	0.388	0.089	0.358	0.282	0.161	0.270	0.714	3.242	0.159	
AUC <sub>0-∞</sub> (μg·h/mL)	0.548	0.262	0.461	0.262	0.459	0.336	0.204	0.298	0.838	4.310	0.213	
MRT <sub>0-11</sub> (h)	9.2	1.9	7.3	1.9	6.7	12.4	1.5	1.3	7.4	18.0	1.3	
MRT <sub>0-∞</sub> (h)	18.1	5.8	12.1	8.5	14.5	16.6	2.4	1.8	11.8	33.6	2.7	
Cl (L/h)	19.0	54.5	14.8	26.0	21.3	29.1	38.3	40.2	14.0	3.8	48.8	
Cl (mL/h/kg)	221	1268	289	510	387	529	660	670	285	63	1028	
V <sub>z</sub> (L)	344	311	183	211	365	175	90	75	164	126	142	
V <sub>z</sub> (L/kg)	4.00	7.32	3.58	4.13	6.64	3.18	1.55	1.25	3.34	2.05	2.99	
Terminal t <sub>1/2</sub> (h)	12.6	3.9	8.5	5.6	11.9	4.1	1.6	1.3	8.1	22.7	2.0	

Table 14.2-07, continued Summary of Pharmacokinetic Parameters for Free Platinum

Patient No.													
8352													
	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Mean ± SE
Dose CDDP (mg)	18.8	18.8	15.2	16.0	16.0	16.0	13.6	13.6	13.6	18.4	16.8	16.8	16.4 ± 0.8
Dose Pt (mg)	12.2	12.2	9.75	10.4	10.6	10.6	8.9	8.9	8.9	12.0	11.0	11.0	10.7 ± 0.5
Body Weight (kg)	80	80	60.5	76	37	37	63	63	63	46	58	58	59.1 ± 2.9
Surface Area (m <sup>2</sup> )	1.96	1.96	1.68	1.93	1.25	1.25	1.69	1.69	1.69	1.46	1.64	1.64	1.64 ± 0.05
C <sub>max</sub> (ng/mL)	118	124	122	60	35	35	98	73	105	85	85	85	95 ± 12
t <sub>max</sub> (h)	0.67	0.08	0.67	2	1	1	1	0	1	1	1	1	0.75 ± 0.12
AUC <sub>0→t</sub> (μg·h/mL)	2.1	1.14	0.242	0.587	0.089	0.089	0.853	0.517	0.512	0.214	0.214	0.214	0.62 ± 0.17
AUC <sub>0→∞</sub> (μg·h/mL)	2.80	1.560	0.273	1.597	0.099	0.099	1.015	0.607	0.562	0.246	0.246	0.246	0.85 ± 0.23
MRT <sub>0→t</sub> (h)	14	18.9	1.0	23.9	0.93	0.93	13.7	5.7	4.6	1.00	1.00	1.00	7.6 ± 1.6
MRT <sub>0→∞</sub> (h)	36	35.7	1.5	104	1.4	1.4	25	10.3	7.3	1.6	1.6	1.6	17.5 ± 5.2
Cl (L/h)	4.0	7.8	35.9	5.2	116.8	8.4	14.6	21.3	44.7	28.4 ± 5.8	28.4 ± 5.8	28.4 ± 5.8	28.4 ± 5.8
Cl (mL/h/kg)	50	98	593	68	3157	133	232	463	771	573 ± 155	573 ± 155	573 ± 155	573 ± 155
V <sub>z</sub> (L)	145	270	54	461	199	199	212	190	219	83	83	83	199.5 ± 23
V <sub>z</sub> (L/kg)	1.81	3.375	0.89	6.07	5.05	5.05	3.37	3.01	4.77	1.43	1.43	1.43	3.49 ± 0.39
Terminal t <sub>1/2</sub> (h)	25	24	1	582	1.2	1.2	17.4	9.0	7.1	1.3	1.3	1.3	11.5 ± 3.2

Attachment 3

Table 1  
Clinical Profile of Patients

Patient No.	Age (yr)	Sex	Body Wt (kg)	Surface Area (m <sup>2</sup> )	Dosing Date(s)	Primary Cancer	Treated Tumor Vol (cm <sup>3</sup> )	Gel Dose (mL)	Admin Dose of CDDP (mg/kg)	Admin Dose of CDDP (mg/m <sup>2</sup> )
1440	50	M	90.5	2.16	17 Feb 93 (Dose 1) 03 Mar 93 (Dose 2)	pancreatic islet cell	160 48	20 6	80 24	37.0 11.1
1441	50	F	73.6	1.89	12 Apr 93 (Dose 1)	gall bladder adenocarcinoma	38	4.8	19.2	10.2
1442	37	F	58.0	1.66	21 Apr 93 (Dose 1) 05 May 93 (Dose 2)	small bowel leiomyosarcoma	137 200	17.2 24	68.8 96	41.4 57.8
1444	60	M	84.1	2.15	17 May 93 (Dose 1)	colorectal adenocarcinoma	274	25	100	46.5
1445	75	F	60.9	1.6	24 May 93 (Dose 1) 08 Jun 93 (Dose 2)	colorectal adenocarcinoma	238 293	25 25	100 100	62.5 62.5
1446	42	M	66.4	1.8	14 Jun 93 (Dose 1) 28 Jun 93 (Dose 2)	gastric leiomyosarcoma	187 37	25 9.3	100 38.4	55.6 21.3
1449	70	F	66.4	1.7	18 Aug 93 (Dose 1)	hepatocellular	775	25	100	58.8
1451	49	M	89.1	2.1	27 Sep 93 (Dose 1)	hepatocellular	3164	25	100	47.6

Table 3a  
Summary of Pharmacokinetic Parameters for Total Pt

	Patient No.													
	1440		1441		1442		1444		1445		1446		1449	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Body Weight (kg)	90.5		73.6		58.0		84.1		60.9		66.4		66.6	89.1
Dose CDDP (mg)	80	24	19	68.8	96		100	100	100	100	100	38.4	100	100
Dose Pt (mg)	52.0	15.6	12.4	44.7	62.4		65.0	65.0	65.0	65.0	25.0	65.0	65.0	65.0
C <sub>max</sub> (µg/mL)	1.49	0.38	0.10	1.09	2.28		0.43	1.49	1.58	0.53	0.35	0.51	0.61	0.90
t <sub>max</sub> (h)	0.33	2.00	6.00	0.33	0.08		6.00	1.00	6.00	24.00*	1.00	20.00*	6.00	2.28
AUC <sub>0-∞</sub> (µg·h/mL)	79.0	16.0	4.65	30.4	40.4		26.7	56.4	59.3	22.1	16.1	17.0	12.9	31.7
AUC <sub>0-∞</sub> (µg·h/mL)	149.8	170.4	48.8	71.4	102.5		99.5	230.8	213.4	1075.8	164.2	41.8	155.7	210.3
MRT <sub>0-∞</sub> (h)	43.4	23.6	23.9	21.6	21.3		33.0	21.2	20.5	25.1	23.8	24.2	12.0	24.5
MRT <sub>0-∞</sub> (h)	132.6	482.7	479.3	88.9	96.4		220.2	158.3	128.8	2447.8	462.9	76.9	252.1	418.9
Cl (L/h)	0.348	0.091	0.253	0.626	0.609		0.653	0.281	0.305	0.060	0.152	1.561	0.417	0.446
(mL/h/kg)	3.84	1.01	3.44	10.81	10.50		7.77	4.62	5.00	0.91	2.29	23.44	4.68	6.53
V <sub>z</sub> (L)	47.3	44.2	121.4	57.0	59.1		144.2	44.7	39.1	148.1	70.4	107.2	104.6	82.3
(L/kg)	0.523	0.488	1.649	0.983	1.019		1.715	0.734	0.642	2.230	1.060	1.610	1.174	1.152
Terminal t <sub>1/2</sub> (h)	94.4	334.4	332.3	63.0	67.4		153.0	109.9	89.0	1698.5	320.7	47.8	173.74	290.3

Table 3b  
Summary of Pharmacokinetic Parameters for Free Pt

	Patient No.													
	1440		1441		1442		1444		1445		1446		1449	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Body Weight (kg)	90.5		73.6		58.0		84.1		60.9		66.4		66.6	89.1
Dose CDDP (mg)	80	24	19	68.8	96		100	100	100	100	38.4	100	100	100
Dose Pt (mg)	52.0	15.6	12.4	44.7	62.4	65.0	65.0	65.0	65.0	65.0	25.0	65.0	65.0	65.0
$C_{max}$ (µg/mL)	1.04	0.05	0.27	0.73	2.01	0.22	1.02	0.43	0.15	0.07	0.10	0.25	0.53	0.17
$t_{max}$ (h)	0.33	0.33	1.00	0.33	0.08	1.00	0.66	1.00	0.33	0.66	0.66	0.33	0.56	0.09
$AUC_{0 \rightarrow \infty}$ (µg·h/mL)	2.76	0.34	0.30	2.44	2.97	1.76	4.13	3.28	1.19	0.50	2.37	1.12	1.93	0.36
$AUC_{0 \rightarrow \infty}$ (µg·h/mL)	8.50	1.05	0.96	3.09	4.17	2.41	8.97	6.81	11.24	0.80	6.03	1.31	4.61	1.04
$MRT_{0 \rightarrow \infty}$ (h)	27.8	17.4	19.8	11.6	10.9	18.8	10.5	13.5	17.7	14.0	24.2	6.19	16.0	1.77
$MRT_{0 \rightarrow \infty}$ (h)	316.3	134.7	131.2	27.7	39.0	43.4	92.1	74.0	453.1	49.2	77.2	10.7	120.7	38.2
Cl (L/h)	6.12	14.8	12.8	14.5	15.0	27.0	7.25	9.55	5.79	31.3	10.8	49.6	17.0	3.73
(mL/h/kg)	67.6	163.4	174.5	249.7	258.0	320.5	119.0	156.8	87.2	471.6	162.5	556.6	232.3	43.6
$V_z$ (L)	2195.4	2111.2	1708.0	584.9	902.3	1605.2	854.7	841.9	2641.5	1874.9	729.6	718.8	1397.4	203.7
(L/kg)	24.3	23.3	23.2	10.1	15.6	19.1	14.0	13.8	39.8	28.3	11.0	8.07	19.2	2.6
Initial $t_{1/2}$ (h)	0.64	2.05	2.14	1.00	0.58	2.31	1.331	1.91	1.68	1.91	1.08	1.90	1.55	0.17
Terminal $t_{1/2}$ (h)	248.8	99.0	92.2	28.0	41.8	41.3	81.8	61.1	316.5	41.5	46.9	10.1	92.4	27.0

Table 4  
Urinary Excretion of Pt in the First 6 Hours  
After Intratumoral Injection of CDDP/Epi Gel

Patient No	Dose No.	<u>Administered Dose</u>		Urine Volume (mL)*	Pt Conc. in Urine (µg/mL)	Pt Excreted (mg)	% of Dose Excreted
		CDDP	Pt				
1440	2	24	15.6	797	1.33	1.06	<del>6.79</del>
1441	1	19	12.35	760	0.50	0.38	3.06
1444	1	100	65	195	4.25	0.83	1.28
1445	1	100	65	165	21.4	3.53	5.43
	2	100	65	370	13.10	4.85	<del>7.46</del>
1446	1	100	65	656	2.41	1.58	2.43
	2	38.4	25.0	909	2.20	2.0	<del>8.0</del>
1449	1	100	65	797	1.23	0.98	1.51
1451	1	100	65	1250	2.76	3.45	5.31

\* Calculated.

## Discussion

The pharmacokinetic profile of CDDP following IV administration has been well characterized. After completion of the injection or infusion, plasma levels of total Pt fall rapidly (initial half-life 10 to 20 minutes), and then decline very slowly (half-lives 2 to 7 days).<sup>2,3</sup> The slow decline has been attributed to binding or reaction of the drug with plasma proteins, with subsequent slow clearance of the platinated proteins. Consistent with this interpretation are the observed levels of free Pt in plasma, which decline rapidly after CDDP administration and exhibit single-exponential kinetics (half-life of 10 to 25 minutes).<sup>4</sup> (Some work has reported biexponential kinetics with half-lives of 8 to 20 and 35 to 80 minutes<sup>2</sup> or approximately 12 minutes and 50 to 60 hours.<sup>5</sup>) The half-life of free Pt following a 5-day continuous IV infusion is reported as somewhat longer, averaging 178 minutes.<sup>6</sup> After IV administration, free Pt has been characterized as a combination of intact CDDP together with the products of reaction between CDDP and water, small peptides, and other low-molecular-weight constituents of plasma.<sup>7,8,9,10</sup> Intact CDDP represents approximately 60% to 80% of the free Pt fraction.<sup>4,9,11</sup> The pharmacokinetics of total Pt and free Pt have been found to

## Attachment 4

Table 1 Patient Characteristics and Baseline Liver Function

Patient No.	Age	Sex	Body Weight (kg)	Body Surface Area (m <sup>2</sup> )	Creatinine Clearance	Total Bilirubin (μmol/L)	Albumin (g/L)	ALT (IU/L)	ALP (IU/L)	INR
1	58	M	66	1.74	92	28	32	82	632	1.28
2	60	M	56	1.55	76	27	27	65	315	1.09
3	52	M	72	1.74	126	36	29	334	196	1.22
4	68	M	59	1.71	65	14	37	92	356	1.10
5	53	M	57	1.66	72	5	36	19	50	1.14
6	75	M	63.5	1.7	55	25	42	59	76	1.07
7	74	F	68	1.71	60	32	25	111	198	1.26
8	68	M	73.5	1.9	63	11	38	110	192	0.98
9	54	F	69.5	1.74	84	11	34	132	231	1.12
10	48	M	68.2	1.75	83	19	31	21	108	1.18

Normal range: Total bilirubin <15 μmol/L, albumin 36-48 g/L, ALT <58 IU/L, ALP 35-100 IU/L, INR 1.0



# Intrahepatic Dosing (CDDP/epi Gel)

Summary of Pharmacokinetic Parameters for Free Pt

	Patient No.											
	6440	6454	6441	6444	6445	6447						
	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Dose 1	Dose 3	Mean	S.E.
Body Weight (kg)	57	68.2	63.5	68	73.5	66.4					66.1	2.3
Surface Area (m <sup>2</sup> )	1.66	1.75	1.7	1.71	1.9	1.74					1.74	0.03
Dose CDDP (mg)		16.0	24.0		40.0	36.0	40.0	40.0	40.0	40.0	28.5	3.5
Dose Pt (mg)		10.4	14.3		26.0	23.4	26.0	26.0	26.0	26.0	21.7	2.5
C <sub>max</sub> (μg/mL)		0.32	0.33		0.62	0.34	0.95	0.10	0.03	0.384	0.119	
(μM)		1.64	1.69		3.18	1.74	4.87	0.51	0.154	1.97	0.61	
t <sub>max</sub> (h)		0.26	0.23		0.83	0.82	1.87	0.47	0.88	0.77	0.21	
AUC <sub>(0→∞)</sub> (μg•h/mL)		0.45	0.61		1.72	0.80	1.21	0.31	0.13	0.75	0.21	
AUC <sub>(0→∞)</sub> (μg•h/mL)		0.71	0.82		4.60	1.09	1.31	0.41	0.16	1.30	0.60	
MRT <sub>(0→∞)</sub> (h)		3.52	5.17		12.45	9.87	3.62	5.56	6.01	6.60	1.26	
MRT <sub>(0→∞)</sub> (h)		29.7	17.7		147.5	33.4	6.70	14.2	13.9	37.6	18.7	
Cl (L/h)		14.6	17.4		5.65	21.5	19.8	63.4	162.5	43.6	21.0	
(mL/h/kg)		214	255		83	292	269	955	2447	645	319	
V <sub>z</sub> (L)		793.2	538.1		1042	1073	401.1	1284	3020	1164	331	
(L/kg)		11.6	7.89		15.3	14.6	5.46	19.3	45.5	17.1	5.0	
Initial t <sub>1/2</sub> (h)		0.47	0.47		0.56	0.96	0.66	1.41	1.72	0.93	0.18	
Terminal t <sub>1/2</sub> (h)		36.6	20.7		124.6	33.9	13.7	13.8	12.7	36.6	15.1	

*Intravenous Infusion  
(Cisplatin Solution)*

Total Pt

Patient ID	980392	973153	980381	B0280327	Average	SD	SE
Dose Pt (mg)	87.500	77.500	87.000	83.500			
Infusion Time (hr)	1.417	1.417	1.000	1.000			
C <sub>max</sub> (uM)	2.46	3.50	3.06	3.50	3.13	0.49	0.25
T <sub>max</sub> (hr)	1.50	1.50	1.00	1.00	1.25	0.29	0.14
AUC <sub>last</sub>	209.94	259.60	204.50	316.43	247.62	52.15	26.07
AUC <sub>INF</sub>	278.00	356.67	284.15	435.94	338.69	74.02	37.01
MRT <sub>last</sub>	112.99	144.28	149.20	146.85	138.33	17.01	8.51
MRT <sub>INF</sub>	241.31	289.38	300.73	293.63	281.26	27.04	13.52
Cl (mL/h/kg)	4.77	3.88	4.25	3.25	4.04	0.64	0.32
V <sub>z</sub> (L)	69.10	63.91	93.79	57.23	71.01	15.95	7.97
V <sub>z</sub> (L/kg)	1.047	1.141	1.302	0.970	1.115	0.143	0.072
Initial t <sub>1/2</sub> (Alpha-HL)	2.47	1.36	0.63	0.96	1.36	0.80	0.40
Terminal t <sub>1/2</sub> (Lambda z)	152.18	203.89	212.32	207.09	193.87	28.01	14.00

*Intravenous Infusion  
(Cisplatin Solution)*

**Ultrafiltrable Pt**

Patient ID	980392	973153	980381	B0280327	Average	SD	SE
Dose Pt (mg)	87.500	77.500	87.000	83.500			
Infusion Time (hr)	1.417	1.417	1.000	1.000			
C <sub>max</sub> (ug)	1.86	2.87	1.87	2.24	2.21	0.47	0.24
T <sub>max</sub> (hr)	1.00	1.50	1.00	1.00	1.13	0.25	0.13
AUC <sub>last</sub>	6.51	6.99	4.58	8.26	6.59	1.53	0.76
AUC <sub>INF</sub>	7.74	7.84	5.11	10.40	7.77	2.16	1.08
MRT <sub>last</sub>	19.90	12.16	14.01	23.67	17.44	5.31	2.65
MRT <sub>INF</sub>	42.89	27.95	28.09	54.27	38.30	12.75	6.37
Cl (mL/h/kg)	171.29	176.5	236.27	136.08	180.0	636.0	18.0
V <sub>z</sub> (L)	775.86	615.22	907.91	614.81	728.45	122.67	61.33
V <sub>z</sub> (L/kg)	11.76	10.98	12.61	10.42	11.44	0.82	0.41
Initial t <sub>1/2</sub> (Alpha-HL)	0.50	0.52	0.42	0.39	0.46	0.06	0.03
Terminal t <sub>1/2</sub> (Lambda z)	47.59	42.46	36.99	53.08	45.03	6.89	3.45

Table 4. Urinary Excretion of CDDP Following Intralesional Administration of CDDP/Epi Gel or Intravenous Infusion of CDDP Solution

Patient No (Dose No)	Platinum Dose (mg)	Amount Pt excreted, 0-72 hr (mg)*	Amount Pt excreted, 0-96 hr (mg)
<b>Intravenous Studies</b>			
980392	87.5	33.2 (37.9%)	35.2 (40.2%)
973153	77.5	26.3 (33.9%)	26.8 (34.6%)
980381	87.0	45.6 (52.4%)	48.1 (55.3%)
B0280327	83.5	27.4 (32.8%)	27.6 (33.1%)
	Mean $\pm$ S.E.	33.1 $\pm$ 4.4 (39.3% $\pm$ 4.5%)	34.4 $\pm$ 4.9 (40.8% $\pm$ 5.1%)
<b>Intrahepatic Studies</b>			
6445-1	23.4	5.88 (25.1%)	na
6445-3	26.0	6.58 (25.3%)	na
6447-1	26.0	5.20 (20.0%)	na
6447-3	26.0	4.13 (15.9%)	na
6444-1	26.0	8.10 (31.2%)	na
6440-1	6.5	1.70 (26.2%)	na
6440-3	7.8	2.82 (36.2%)	na
6441-1	18.2	3.24 (17.8%)	na
6441-3	18.2	2.30 (12.6%)	na
6454-1	10.4	2.62* (25.2%)	na
6454-3	15.6	4.16 (26.7%)	na
	Mean $\pm$ S.E.	4.25 $\pm$ 0.60 (23.8% $\pm$ 2.1%)	

Values in parentheses are percent of platinum dose.

\* 16-20 hr urine sampling missed

# Attachment 5

## Final Report

Validation of a Graphite Furnace Atomic Absorption Spectroscopic  
Method for the Analysis of Platinum from Cisplatin in  
Human Plasma and Plasma Ultrafiltrate

PREPARED FOR:  
Matrix Pharmaceutical, Inc.

COVANCE STUDY NUMBER:  
6877-100

ISSUE DATE:  
April 30, 2001

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Initials/Date ph 4-30-01

## INTRODUCTION

The Inorganic Chemistry Group of Covance has developed and validated an atomic absorption spectrophotometric method for the determination of platinum from cisplatin in human plasma, and human plasma ultrafiltrate (PUF). The applicable method used for this validation was designated as Covance method procedure MP-PTPL-MA, effective date 7/13/95.

## OBJECTIVE

The objective of this study was to validate a method for the quantification of platinum from cisplatin in human plasma, and human plasma ultrafiltrate (PUF).

## REGULATORY COMPLIANCE

This study was conducted at Covance (a GLP compliant facility).

## REFERENCE AND MATRIX MATERIALS

### Reference Material

#### Identification

The reference material used for the duration of this validation was obtained commercially, and described as cisplatin, (CDDP or cis platinum (II) diammine dichloride) MW =300.0, Lot number 96H3487, purity 100%, expiration November 26, 1998, Sigma Chemical Co. Abbreviated name for cisplatin used in this study report was cis.

#### Storage Condition

The reference material was stored protected from light at ambient temperature.

#### Purity, Stability, and Characterization

Information on purity, stability, and characterization determinations that define the reference material is contained in the study contents.

#### Disposition

Any unused reference material will be discarded after issuance of the final report, according to Covance SOP, unless otherwise directed by the sponsor.

### Matrix Material

The matrix material was defined as human plasma, Lot Nos.: M48934, M50365, Biochemed Corporation, Winchester, VA.

### Safety Precautions

Safety precautions were as required by Covance SOPs and policies.

## EXPERIMENTAL DESIGN

### Principles of the Method

An aliquot of plasma was diluted 10-fold in a magnesium nitrate-ammonium chloride-Triton matrix modifier. PUF samples were analyzed directly, without dilution. The samples were analyzed for platinum by atomic absorption spectrophotometry directly without predigestion. Peak area absorbance values were obtained from the graphite furnace equipped with Zeeman background correction.

### Apparatus and Materials

- Vials, cryogenic, sterile, 2- to 5-mL capacity, Corning
- Volumetric flasks, assorted sizes, Corning
- Volumetric pipettes, Class A, assorted sizes, Corning
- Eppendorf pipettes, Model 4810, Model 4780, Brinkmann
- Eppendorf Combitips, various sizes, Brinkmann
- Pipette tips, plastic, 100  $\mu$ L, various sources
- Transfer pipettes, polyethylene, Fisher Scientific
- Zeeman atomic absorption spectrometer, Model 4100ZL, with computer and autosampler, Perkin-Elmer
- Data processing, 4100PC Version 6.20, Perkin-Elmer
- Analytical balance, four-place, Model AE 160, Mettler Instrument Corporation
- Balance, two-place, Model 7202, Fisher Scientific
- Centrifuge tube, polyethylene, 50 mL, Fisher Scientific
- Graphite tubes, pyrolytically coated, THGA, Perkin-Elmer
- Graphite furnace autosampler cups, Fisher Scientific
- Biohazard bags, Baxter Scientific Products
- Vortex, Model 16700 MaxiMix 1, Barnstead/Thermolyne Printer, Model LQ 850, Epson
- Centrifuge, Model K, International Equipment Co.

### Reagents

- Double-deionized (DDI) water, in-house
- Concentrated hydrochloric acid (Ed), J.T. Baker
- Triton X-100, Fisher Scientific
- Ammonium chloride,  $\text{NH}_4\text{Cl}$ , ACS grade, Fisher Scientific
- Magnesium nitrate [ $\text{Mg}(\text{NO}_3)_2$ ], 10,000  $\mu\text{g/mL}$ , Spex Industries, Incorporated
- Antifoam B emulsifier, Sigma Chemical Company

Note: Equivalent materials may be substituted.

## PROCEDURES

### Preparation of Matrix Modifier

(0.15% Triton, 100 µg/mL  $\text{Mg}(\text{NO}_3)_2$ , and 0.50%  $\text{NH}_4\text{Cl}$ )

0.75 g Triton X-100 surfactant was weighed into a 500-mL volumetric flask. An appropriate amount of double-deionized (DDI) water was added to the flask and swirled to dissolve the surfactant. The contents were swirled until the surfactant was dissolved. 5.0 mL of a commercially prepared 10,000 µg/mL  $\text{Mg}(\text{NO}_3)_2$  solution was volumetrically added to the flask. 2.5 g of  $\text{NH}_4\text{Cl}$  was added to the flask and the contents were swirled to dissolve the salt. 3 to 4 drops of Antifoam B emulsifier were added to the flask and the contents were swirled. The solution was diluted to a final volume 500-mL with DDI water, stoppered, and mixed well. The solution was stored at ambient temperature.

### Preparation of Standard Solutions

The stock standard solutions for cisplatin were prepared in duplicate. The calibration working standards, and the pooled quality control (QC) samples, were prepared from different stock standard solutions.

#### Stock Standard Solution (100,000 ng Cisplatin/mL)

10.0 mg of cisplatin was weighed into a 100-mL volumetric flask and the weight was recorded. Approximately 50 mL of DDI water, and two to three drops of concentrated HCl, were added to dissolve the compound. Once dissolved, the solution was diluted to volume with DDI water, and mixed thoroughly. This standard was prepared fresh and used within one month.

#### Intermediate Stock Standards (10,000 ng Cisplatin/mL)

10 mL of the 100,000 ng cisplatin/mL stock standard solution was volumetrically added to a 100-mL volumetric flask. Two to three drops of HCl were added. The standard solution was diluted to volume with DDI water and mixed thoroughly.

#### Intermediate Stock Standards (1,000 ng Cisplatin/mL)

10 mL of the 10,000 ng cisplatin/mL stock standard solution was volumetrically added to a 100-mL volumetric flask. Two to three drops of HCl were added, the standard solution was diluted to volume with DDI water and mixed thoroughly.

These standards were prepared fresh and used within one month.

The stock and intermediate standard solutions were stored at room temperature and protected from light when not in use.

### Preparation of Calibration Working Standards

The calibration curve standards for both plasma and plasma ultrafiltrate (PUF) matrices were derived from the cisplatin stock and intermediate stock standards. Plasma standards were prepared for a calibration range of 150 to 5000 ng cisplatin/mL plasma. PUF standards were prepared for a calibration range of 30 to 400 ng cisplatin/mL PUF.

## Preparation of Quality Control (QC) Samples

Plasma (concentrations were of cisplatin)

Low QC (500 ng/mL). Using an Eppendorf microliter pipette, 25.0  $\mu$ L of the 100,000 ng/mL stock standard was added to a 5-mL volumetric flask. The QC was diluted to volume with blank human plasma and mixed thoroughly. Stored QC samples at -20°C.

Medium QC (2,000 ng/mL). Using an Eppendorf microliter pipette, 100  $\mu$ L of the 100,000 ng/mL stock standard was added to a 5-mL volumetric flask. QC was diluted to volume with blank human plasma and mixed thoroughly. Stored QC samples at -20°C.

High QC (4,000 ng/mL). Using an Eppendorf microliter pipette, 200  $\mu$ L of the 100,000 ng/mL stock standard was added to a 5-mL volumetric flask. QC was diluted to volume with blank human plasma, and mixed thoroughly. Stored QC samples at -20°C.

Over Calibration QC (25,000 ng/mL). Using an Eppendorf microliter pipette, 1,250  $\mu$ L of the 100,000 ng/mL stock standard was added to a 5-mL volumetric flask. The QC was diluted to volume with blank human plasma and mixed thoroughly. Stored QC samples at -20°C.

Lower Limit of Quantitation (LLOQ) QC (150 ng/mL). Using an Eppendorf microliter pipette, 30.0  $\mu$ L of the 10,000 ng/mL stock standard was added to a 2-mL volumetric flask. The QC was diluted to volume with blank human plasma and mixed thoroughly. Stored QC samples at -20°C.

PUF (concentrations were of cisplatin)

Low QC (90.0 ng/mL). Using an Eppendorf microliter pipette, 180  $\mu$ L of the 1,000 ng/mL stock standard was added to a 2-mL volumetric flask. The QC was diluted to volume with blank human PUF and mixed thoroughly. Stored QC samples at -20°C.

Medium QC (240 ng/mL). Using an Eppendorf microliter pipette, 48.0  $\mu$ L of the 10,000 ng/mL stock standard was added to a 2-mL volumetric flask. The QC was diluted to volume with blank human PUF and mixed thoroughly. Stored QC samples at -20°C.

High QC (480 ng/mL). Using an Eppendorf microliter pipette, 96.0  $\mu$ L of the 10,000 ng/mL stock standard was added to a 2-mL volumetric flask. The QC was diluted to volume with blank human PUF and mixed thoroughly. Stored QC samples at -20°C.

Over Calibration QC (3,000 ng/mL). Using an Eppendorf microliter pipette, 150  $\mu$ L of the 100,000 ng/mL stock standard was added to a 5-mL volumetric flask. The QC was diluted to volume with blank human PUF and mixed thoroughly. Stored QC samples at -20°C.

Lower Limit of quantitation (LLOQ) QC (30.0 ng/mL). Using an Eppendorf microliter pipette, 30.0  $\mu$ L of the 1,000 ng/mL Stock Standard was added to a 1-mL volumetric flask. The QC was diluted to volume with blank human PUF and mixed thoroughly. Stored QC samples at -20°C.

## VALIDATION STUDY

### Analytical Runs

**Plasma** : On each of the first 3 days, the following were analyzed.

- Calibration curves in duplicate
- 6 replicates of the QCs containing low, medium, and high spikes
- Two blanks

This gave n=18 for each control level.

- Day 1 contained 6 replicates of the LLOQ QC
- Day 2 contained 3 replicates of the over-calibration QC.
- Day 3 contained a two cycle freeze/thaw stability (low and high QCs in triplicate.)

**PUF**: On each of the first 3 days, the following were analyzed.

- Calibration curves in duplicate
- 6 replicates of the QCs containing low, medium, and high spikes
- Two blanks

This gave n=18 for each control level.

- Day 1 contained 6 replicates of the LLOQ QC
- Day 2 contained 3 replicates of the over-calibration QC.
- Day 3 contained two cycle freeze/thaw stability (low and high QCs in triplicate.)

### Assay Criteria

The percent relative standard deviation (%RSD) for the standards and QCs must be less than or equal to 15% (20% at the LLOQ) for the method to be considered acceptable. The mean predicted concentrations for the standards and QCs must be within  $\pm 15\%$  of their nominal values ( $\pm 20\%$  for the lowest standard).

## RESULTS AND DISCUSSION

### Plasma

#### Specificity

No detectable levels of platinum were found in the plasma lot during the analysis of blank working standards.

#### Linearity

The calibration curves were linear in the concentration range of 150 to 5,000 ng cisplatin/mL (97.5 to 3250 ng Pt/mL) with  $r^2$  values of 0.9979 or greater (Table 3). Cisplatin concentration is converted to platinum concentration using the equation:  $[195.08_{(M.W. \text{ platinum})} / 300.0_{(M.W. \text{ cisplatin})}] \times \text{concentration cisplatin} = \text{platinum concentration}$  or  $[0.6503 \times \text{cisplatin concentration} = \text{platinum concentration}]$

**Sensitivity**

The LLOQ was determined to be 150 ng cisplatin/mL (97.5 ng Pt/mL), the lowest standard concentration in the linearity curve (Table 14).

**Precision**

The within-run precision was 6.7% or less (Tables 4-6). The between-run precision was 9.0% or less (Tables 4-6).

**Accuracy**

The mean observed concentrations for the 500, 2,000 and 4,000 ng cisplatin/mL QC samples were, respectively, 3.6%, 4.5% and 2.5% of the nominal concentration (Tables 4-6). The mean concentration for the 25,000 ng cisplatin/mL over-calibration QC samples was 4.0% of nominal (Table 10).

**Stability**

The mean percent deviation from nominal for two freeze/thaw stability cycles ranged from 10.2% to 4.0% (Table 12)

**PUF****Specificity**

No detectable levels of platinum were found in the plasma ultrafiltrate lot during the analysis of blank working standards.

**Linearity**

The calibration curves were linear in the concentration range of 30.0 to 600 ng cisplatin/mL (19.5 to 260 ng Pt/mL) with  $r^2$  values of 0.9986 or greater (Table 3)

**Sensitivity**

The LLOQ was determined to be 30.0 ng cisplatin/mL (19.5 ng Pt/mL), the lowest standard concentration in the linearity curve (Table 15).

**Precision**

The within-run precision was 4.2% or less (Tables 7-9). The between-run precision was 4.0% or less (Tables 7-9).

**Accuracy**

The mean observed concentrations for the 90.0, 240 and 480 ng cisplatin/mL QC samples were, respectively, 1.4%, 4.2% and 2.9% of the nominal concentration (Tables 7-9). The mean concentration for the 3,000 ng cisplatin/mL over-calibration QC samples was -2.3% of nominal (Table 11)

**Stability**

The mean percent deviation from nominal for two freeze/thaw stability cycles ranged from 0.0% to 3.3% (Table 13).

**Quantitation Limit (QL), Detection Limit (DL), and Standard Error of Regression (SER)**

The limit of detection was determined using the following equations per sponsors request:

$$QL = 5 \times \text{SER of the linearity curve}$$

$$DL = 2 \times \text{SER of the linearity curve}$$

For plasma, the SER of the linearity data of Table 1 is 25.2.

For plasma ultrafiltrate, the SER of the linearity data of Table 2 is 3.53.

**Table 1**  
**Calibration Standard Results for Cisplatin in Plasma**

Standard (ng/mL)	Day	Concentration (ng/mL)	Summary Statistics	
150	1	122		
		158		
	2	132		
		150	Mean	138
	3	125	SD	14.3
		142	RSD%	10.3
			DEV%	-8.0
450	1	425		
		479		
	2	505		
		430	Mean	463
	3	478	SD	30.9
		461	RSD%	6.7
			DEV%	2.9
750	1	800		
		764		
	2	766		
		747	Mean	769
	3	743	SD	24.0
		796	RSD%	3.1
			DEV%	2.5
1500	1	1530		
		1570		
	2	1510		
		1530	Mean	1550
	3	1570	SD	31.0
		1590	RSD%	2.0
			DEV%	3.3

SD            Standard deviation.  
RSD%       Per cent relative standard deviation.  
DEV%       Per cent deviation from nominal.

**Table 1 (Continued)**  
**Calibration Standard Results for Cisplatin in Plasma**

Standard (ng/mL)	Day	Concentration (ng/mL)	Summary Statistics	
3000	1	3010		
		3030		
	2	3060		
		3020	Mean	3030
	3	3040	SD	17.5
		3040	RSD%	0.6
			DEV%	1.0
	1	4900		
		4900		
5000	2	5000		
		4840	Mean	4890
	3	4760	SD	84.0
		4950	RSD%	1.7
			DEV%	-2.2

SD        Standard deviation.  
RSD%    Per cent relative standard deviation.  
DEV%    Per cent deviation from nominal.

**Table 2 (Continued)**  
**Calibration Standard Results for Cisplatin in Plasma Ultrafiltrate**

Standard (ng/mL)	Day	Concentration (ng/mL)	Summary Statistics	
400	1	408		
		399		
	2	411		
		399	Mean	407
	3	405	SD	7.3
		418	RSD%	1.8
			DEV%	1.8
600	1	598		
		587		
	2	596		
		583	Mean	590
	3	592	SD	6.3
		584	RSD%	1.1
			DEV%	-1.7

SD        Standard deviation.  
RSD%    Per cent relative standard deviation.  
DEV%    Per cent deviation from nominal.

**Table 3**  
**Summary of Standard Curve Data**

Analysis	Slope	Intercept	r <sup>2</sup>	Matrix
Day 1	5.60 x 10 <sup>-5</sup>	0.00417	0.9987	Plasma
Day 2	5.36 x 10 <sup>-5</sup>	0.00195	0.9988	Plasma
Day 3	5.66 x 10 <sup>-5</sup>	0.00194	0.9979	Plasma
Day 1	5.63 x 10 <sup>-5</sup>	-0.00038	0.9995	PUF
Day 2	5.87 x 10 <sup>-5</sup>	0.00011	0.9986	PUF
Day 3	5.78 x 10 <sup>-5</sup>	0.00257	0.9987	PUF

**Table 4**  
**Low Quality Control (500 ng Cisplatin/mL) Results for Plasma**

Day	Concentration (ng/mL)	Summary Statistics	
1	550		
	532		
	568	Mean	544
	532	SD	31.2
	497	RSD%	5.7
	586	DEV %	8.8
2	523		
	617		
	542	Mean	545
	523	SD	36.4
	542	RSD%	6.7
	523	DEV%	9.0
3	443		
	478		
	461	Mean	464
	443	SD	20.6
	461	RSD%	4.4
	496	DEV%	-7.2

**Overall**

Mean	518
SD	46.5
RSD%	9.0
DEV%	3.6
n	3

SD	Standard deviation.
RSD%	Per cent relative standard deviation.
DEV%	Per cent deviation from nominal.

**Table 5**  
**Medium Quality Control (2000 ng Cisplatin/mL) Results for Plasma**

Day	Concentration (ng/mL)	Summary Statistics	
1	1980		
	2000		
	2140	Mean	2070
	2080	SD	65
	2100	RSD%	3.2
	2120	DEV%	3.5
2	2040		
	2170		
	2150	Mean	2090
	2050	SD	57
	2070	RSD%	2.7
	2050	DEV%	4.5
3	2140		
	2140		
	2090	Mean	2100
	2090	SD	32
	2070	RSD%	1.5
	2070	DEV%	5.0
<b>Overall</b>			
	Mean	2090	
	SD	15	
	RSD%	0.7	
	DEV%	4.5	
	n	3	

---

SD      Standard deviation.  
RSD%    Per cent relative standard deviation.  
DEV%    Per cent deviation from nominal.

**Table 6**  
**High Quality Control (4000 ng Cisplatin/mL) Results for Plasma**

Day	Concentration (ng/mL)	Summary Statistics	
1	4070		
	4170		
	4030	Mean	4030
	4050	SD	192
	3660	RSD%	4.8
	4190	DEV%	0.8
2	4200		
	4260		
	4140	Mean	4200
	4160	SD	46
	4200	RSD%	1.1
	4240	DEV%	5.0
3	4070		
	4000		
	4010	Mean	4080
	4120	SD	66
	4150	RSD%	1.6
	4140	DEV%	2.0
<b>Overall</b>			
	Mean	4100	
	SD	87	
	RSD%	2.1	
	DEV%	2.5	
	n	3	

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SD      Standard deviation.  
RSD%    Per cent relative standard deviation.  
DEV%    Per cent deviation from nominal.

**Table 7**  
**Low Quality Control (90 ng Cisplatin/mL) Results for Plasma Ultrafiltrate**

Day	Concentration (ng/mL)	Summary Statistics	
1	89.5		
	91.3		
	93.1	Mean	92.5
	89.5	SD	2.91
	96.6	RSD%	3.1
	94.9	DEV %	2.8
2	90.1		
	90.1		
	86.7	Mean	91.9
	95.3	SD	3.45
	95.3	RSD%	3.8
	93.6	DEV%	2.1
3	90.7		
	92.4		
	90.7	Mean	89.5
	85.5	SD	2.61
	87.2	RSD%	2.9
	90.7	DEV%	-0.6
<b>Overall</b>			
	Mean	91.3	
	SD	1.59	
	RSD%	1.7	
	DEV%	1.4	
	n	3	

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SD      Standard deviation.  
RSD%    Per cent relative standard deviation.  
DEV%    Per cent deviation from nominal.

**Table 8**  
**Medium Quality Control (240 ng Cisplatin/mL) Results for Plasma Ultrafiltrate**

Day	Concentration (ng/mL)	Summary Statistics	
1	255		
	260		
	262	Mean	252
	239	SD	9.0
	244	RSD%	3.6
	251	DEV%	5.0
2	245		
	250		
	250	Mean	250
	249	SD	2.6
	252	RSD%	1.0
	252	DEV%	4.2
3	248		
	252		
	255	Mean	249
	243	SD	4.3
	250	RSD%	1.7
	246	DEV%	3.8
<b>Overall</b>			
	Mean	250	
	SD	1.5	
	RSD%	0.6	
	DEV%	4.2	
	n	3	

SD        Standard deviation.  
RSD%    Per cent relative standard deviation.  
DEV%    Per cent deviation from nominal.

**Table 9**  
**High Quality Control (480 ng Cisplatin/mL) Results for Plasma Ultrafiltrate**

Day	Concentration (ng/mL)	Summary Statistics	
1	518		
	527		
	525	Mean	509
	493	SD	16.1
	493	RSD%	3.2
	498	DEV%	6.0
2	487		
	494		
	503	Mean	496
	496	SD	5.4
	494	RSD%	1.1
	499	DEV%	3.3
3	440		
	480		
	469	Mean	477
	492	SD	20.1
	488	RSD%	4.2
	492	DEV%	-0.6
<b>Overall</b>			
	Mean	494	
	SD	16.1	
	RSD%	3.3	
	DEV%	2.9	
	n	3	

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SD      Standard deviation.  
RSD%    Per cent relative standard deviation.  
DEV%    Per cent deviation from nominal.